DISSERTATION ON

TO COMPARE THE SAFETY AND EFFICACY OF GLIMEPIRIDE – METFORMIN WITH VILDAGLIPTIN - METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL

Dissertation submitted to

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MADHURANTHAGAM.

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CERTIFICATE

This is to certify that Dr.P.KALAISELVI, a Post Graduate student in the Department of Pharmacology has carried out the work titled "**TO COMPARE THE SAFETY AND EFFICACY OF GLIMEPIRIDE – METFORMIN WITH VILDAGLIPTIN - METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL"** under the guidance of **Dr.PURABI ROY.,M.D.,** Professor and Head, Dept. of Pharmacology, towards the partial fulfilment of regulations laid down by the Tamilnadu Dr.M.G.R Medical University, Chennai, Tamilnadu, India, for the award of Doctor of Medicine (M.D.,) in Pharmacology.

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DECLARATION

I declare that the dissertation entitled **"TO COMPARE THE SAFETY AND EFFICACY OF GLIMEPIRIDE – METFORMIN WITH VILDAGLIPTIN - METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS IN A TERTIARY CARE HOSPITAL"** submitted by me for the Degree of M.D is the record work carried out by me during the period of January 2014 to March 2015 under the guidance of Dr.PURABI ROY.,M.D., PROFESSOR and H.O.D of Pharmacology, Karpaga Vinayaga Institute of Medical Sciences and Research Centre and has not formed the basis of any Degree ,Diploma, Fellowship, titles in this or any other University or other similar Institution of Higher learning.

Signature of the candidate

Place: **Dr.P.KALAI SELVI**

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INTRODUCTION

Diabetes Mellitus is a common "Metabolic Disorder" described by hyperglycemia and modified metabolism of lipids, proteins, and sugars which is because of total or relative lack of insulin or insulin resistance.

Diabetes is not an epidemic any longer but rather has transformed into a pandemic for the entire world.[1] The all inclusive study reported that diabetes is aggravating almost 10% of the inhabitants.[3] According to the World Health Organization (WHO) projections, the prevalence of diabetes is liable to expand by 35% by the year 2025.[4] India has a "high prevalance of diabetes" and the numbers are still increasing.[5]

Past studies have shown that early serious glycemic control diminishes the danger of diabetic related consequences both " micro & macro vascular" . In vivo studies have uncovered that "oxidative stress" happens prior to the development of "complications of diabetes".

Type 2 diabetes mellitus patients are more inclined to cardiovascular complications, when contrasted with non-diabetic patients.[5] Dyslipidemia, is commonly seen in patients with type 2 diabetes. [6]

As indicated by different rules for T2DM treatment, metformin is prescribed when food and life style interventions alone are not able to keep up blood glucose control at target levels.[7,8] Failure of monotherapy after some time recommends the requirement for multiple drugs to keep up the glycemic goals.[9] Several oral treatments are recommended for utilization – metformin, though they may be connected with side effects.[10]

Sulfonylureas are connected with hypoglycemia and increase in weight; thiazolidinediones are connected with weight increase, fluid retention, congestive heart failure and α-glucosidase inhibitors are connected with "abdominal discomfort, increased intestinal gas, and diarrhea."[10] Given these contemplations, there remains a considerable requirement for an agent that could enhance β-cell capacity, enhance glycaemic control, and have less unfavorable impact.

" Dipeptidyl peptidase-4 (DPP-4) inhibitors" are a new class of oral anti-diabetic agents that increase circulating concentrations of the glucagon-like peptide-1 (GLP-1).[11] GLP-1 is released after meals but gets degraded by dipeptidyl peptidase-4 (DPP-4) rapidly. The DPP-4 inhibitors block the rapid inactivation of GLP-1 and improve glycaemic control.[12] It has been indicated that dipeptidyl peptidase-4 inhibitors (DPP4i) are superior to traditional oral hypoglycemic agents in terms of efficacy and tolerability.[13-14]

"In the 2009 position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for the treatment of hyperglycemia in type 2 diabetes." DPP4i were not well-accepted treatments and not suggested in the principle treatment steps.[15] However, the 2012 statement of the ADA and EASD included DPP4i as second-choice medication when metformin therapy failed.[16] Several DPP-4 inhibitors have been produced, including vildagliptin, sitagliptin, and saxagliptin.[17] When it comes to combination therapy, various agents demonstrated greater glycemic control and tolerance in Asian patients with T2DM who had insufficient glycemic control with metformin or glimepiride. [18,19]

Vildagliptin is a powerful, oral and specific DPP-4 inhibitor for the treatment of patients with type 2 DM.[7] Metformin and Vildagliptin have independent glucose decreasing properties and may expand GLP-1 levels by working through other alternate methods. "The combination of metformin and glimepiride is a well established treatment regimen for type 2 DM."

Hence, the present study was undertaken to compare the efficacy and safety of vildagliptin-metformin and glimepiride-metformin treatment in type 2 diabetic patients.

AIM OF THE STUDY

- To compare the safety and efficacy of Glimepiride – Metformin with Vildagliptin - Metformin in type 2 diabetes mellitus patients in a tertiary care hospital.

REVIEW OF LITERATURE

"Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia." Diabetes mellitus, the most common endocrine disease is represented by metabolic abnormalities due to relative or absolute deficiency of insulin and or insulin resistance resulting in hyperglycemia and associated with micro and macro vascular complications.[1]

The monetary burden of DM approximated $132 billion in 2002, including direct medicinal and treatment costs and in addition other expenses "attributed to disability and mortality". DM is the major cause of loss of vision in adults, and "end stage renal disease".[20] The cardiovascular disease is responsible for 66% of death in people with type 2 DM. Despite the endeavor to control hyperglycemia, the challenge remains in decreasing secondary complications and enhancing the quality of life of patients with DM.

Research and drug advancement endeavors in the course of recent decades have given profitable data that applies specifically to enhance the results in patients with DM.[20]

PREVALENCE:

The worldwide prevalance of diabetes in 2008 was evaluated to be 10% in adults aged >25 years. The prevalence of diabetes was most astounding in

Eastern Mediterranean Region and the Region of Americas (11% for both genders). The economically weaker nations over the world indicated prevalence of 8%.

In India, the results of prevalence showed that 37.7 million people of diabetes were present among which 21.4 were in urban area and 16.3 in rural area. The total mortality due to diabetes was 1.09 lakh and around 2.2 million DALY (Disability Adjusted Life Year) lost due to the disease. [21]

EPIDEMIOLOGY:

"The prevalence of type 2 DM is ever increasing. There is a likelihood of one individual undiagnosed for each three persons currently diagnosed with the disease. Multiple risk factors for the development of type 2 DM include family history (i.e., parents or siblings with diabetes), over weight (i.e., ≥20% over perfect body weight, or body mass index [BMI] ≥25 kg/m2); continual physical inactivity; race or ethnicity; already recognized impaired glucose tolerance or impaired fasting glucose , hypertension (≥140/90 mm Hg in grown-ups); High-Density Lipoprotein (HDL) cholesterol ≤35 mg/dL and/or a Triglyceride level ≥250 mg/dL; history of gestational DM or delivery of over weight babies measuring >4 kg (9 lb); history of vascular illness; vicinity of acanthosis nigricans; and polycystic ovary."

The cause is unknown in many cases of type-2 DM and so it is not certain if it indicates a few or many "independent disorders" manifesting as hyperglycemia.

Classification of diabetes mellitus:[25]

1. Diabetes mellitus type 1

A. Autoimmune

B. Idiopathic

2. Diabetes mellitus type 2

1. Insulin resistance predominates over the relative defects in hormone secretion

2. Defects in insulin secretion predominate over the presence of insulin resistance

3. Other forms

A. Hereditary imperfections in β cell capacity

1. Chromosome 12, HNF-1α (MODY 3)

2.Chromosome 7, glycosidase (MODY 2)

B. Hereditary imperfections in insulin activity

1. Type A insulin resistance

2. Leprechaunism

C. Ailment of the exocrine pancreas

Pancreatitis, Cystic fibrosis, Hemochromatosis, Fibrocalcific pancreatopathy

D. Endocrinopathies

Acromegaly, Cushing disorder, Glucagonoma, Pheochromocytoma, Hyperthyroidism

E. Pharmacologically or artificially prompted

Pentamidine, Nicotinic corrosive, Glucocorticoids, Thyroid hormones, Diazoxide, β-adrenergic agonists, Thiazides, Dilantin, α interferon

F. Diseases

Intrinsic rubella, Cytomegalovirus

G. Rare types of immune system diabetes

Stiff-man syndrome, Antibodies against insulin receptors

H. Other syndromes

Down’s , Klinefelter’s, Turner’s, Wolfram disorders

Friedreich ataxia, Huntington's chorea

4. Pregnancy induced diabetes mellitus

PATHOGENESIS OF DIABETES MELLITUS:

Pathogenesis of type 2 diabetes mellitus:-

"Type 2 DM is the most common form of diabetes, representing around 90 to 95% of every diagnosed case of diabetes. In type 2 diabetes the body does not produce enough insulin or the cells ignore the insulin produced.[26] Type 2 diabetes is because of deficient insulin generation from beta cells along with insulin resistance.[27] Insulin resistance which is the failure of cells to react satisfactorily to typical levels of insulin essentially within the muscles, liver and fat tissue."[28]

"Other possible vital components connected with type 2 diabetes and insulin resistance include: enhanced breakdown of lipids, absence of incretin, high glucagon levels in the blood, increased salt and water retention by the kidneys.[29] However not all individuals with insulin resistance develop diabetes, since an impairment of insulin secretion by pancreatic beta cells is also required."[27]

SIGNS AND SYMPTOMS:

The manifestations of diabetes are "Polyuria (frequent urination), Polydipsia (increased thirst) and Polyphagia (increased craving)".Symptoms develop fast (weeks or months) in type 1 diabetes while in type 2 diabetes they develop slowly. High blood glucose can result in changes within the lens leading

to decrease in vision. Obscured vision is a typical complaint of the patient and hence diabetes (type 1 or type 2) should always be suspected. "Various skin rashes can occur in diabetes that are collectively known as diabetic dermadromes."[30]

DIAGNOSIS OF DIABETES:

Diagnosis of diabetes at a prior stage is imperative in averting diabetes related complications. The tests ordinarily used to analyze diabetes are fasting blood glucose, postprandial blood glucose and HbA1c.

(A) Measurement of blood glucose

The current WHO indicative criteria for diabetes incorporate estimation of blood glucose level. "The fasting plasma glucose greater than 7.0 mmol/l (126 mg/dl) or 2 hour plasma glucose more greater than 11.1 mmol/l (200 mg/dl) demonstrate that the individual may have diabetes."[31] With great glycemic control, a few life threatening consequences can be prevented.[32]

(B) Glycated Hemoglobin (HbA1c)

"Glycated hemoglobin (HbA1c)" is the best indicator of long term glycemic control, since it symbolizes the normal blood glucose levels over a period of time.[33] Glycemic control is defined as excellent if the measured HbA1c

is < 6.5 %, very good if HbA1c is 6.5 to 7.0 %, good if HbA1c is 7.1 to 7.5 %, acceptable if HbA1c is 7.6 to 8.0 % and poor if HbA1c is > 8.0 %.[34]

(C) C-peptide

C-peptide has been broadly acknowledged as the most fitting measure of lingering beta cell function since it is discharged on an equimolar concentration to insulin and is not removed in the liver through first pass metabolism.[35] Since the pancreas delivers one C-peptide particle for each insulin atom it fabricates, patients with better glucose control will likewise have higher C-peptide levels.[36] "Fasting C-peptide level < 0.6 ng/ml is considered as a marker of poor insulin hold. Subsequently C-peptide is a helpful aide in starting treatment to forestall complications."[37]

(D) Oral glucose tolerance test (OGTT)

OGTT is utilized as a symptomatic test as fasting plasma glucose alone neglects to analyze more or less 30% of cases.[31]

COMPLICATIONS OF DM

Diabetes is customarily known as a "silent disease" showing no side effects until it advances to extreme target organ damage.[38]

Acute complications of diabetes

These incorporate “diabetic ketoacidosis (DKA) and nonketotic hyperosmolar state (NKHS)”. While the first is seen essentially in people with type 1 DM, the latter is predominant in people with “type 2 DM”.

“In DKA, insulin inadequacy is combined with counter regulatory hormone abundance (glucagon, catecholamines, cortisol and development hormone). The decreased proportion of insulin to glucagon advances gluconeogenesis, glycogenolysis and ketone body arrangement in the liver further enhances free unsaturated fats and amino acid delivery from fat and muscle to the liver. Ketosis results from a marked increment in free unsaturated fat discharge from adipocytes because of enhanced lipolysis. In DKA, nausea and vomiting are present. Lethargy and CNS depression may advance into coma in severe DKA. Cerebral edema, is seen most commonly in children.”

NKHS is most generally found in elderly people with type 2 DM. Its most important components are “polyuria, orthostatic hypotension and a mixture of neurological side effects including alteration in the mental state, lethargy, obtundation, seizure and coma like state.” Insulin lack and deficient fluid intake are the reasons for NKHS. Insulin lack prompts hyperglycemia, which causes an osmotic diuresis prompting depletion of intravascular volume.

Chronic complications of diabetes mellitus[40]

Long term effects of diabetes can be isolated into vascular and nonvascular intricacies. The "vascular complications" are further subdivided into "microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (CAD, peripheral vascular disorders and cerebrovascular disorders)." Nonvascular complexities include, "gastroparesis", loss of sexual function and skin changes. As a result, DM is the most widely recognized "reason for loss of vision, crippling neuropathies, cardiovascular and cerebral diseases." Treating the consequences of diabetes cost more than controlling the illness.

Diabetic retinopathy:

"Diabetic retinopathy" happens in 3/4 of all persons having diabetes for over 15 years and is the most widely recognized reason for visual impairment. There is appearance of "retinal vascular lesions" leading to development of new vessels.

Neuropathy:

Patients with diabetes have some level of "neuropathy", which can be "polyneuropathy, mononeuropathy, and/or autonomic neuropathy." In polyneuropathy there is loss of peripheral sensation which, when combined with

“weakened microvascular and macrovascular capacity”, can lead to ulcers, the main source of “non traumatic amputation”.

Nephropathy:

This is a major cause of end stage renal disease. There are “glomerular hemodynamic anomalies” resulting in “glomerular hyperfiltration, prompting glomerular damage as evidenced by microalbuminuria.” “There is overt proteinuria, decreased glomerular filtration rate and end stage renal disease”.

Cardiovascular morbidity and mortality:

In “Diabetes Mellitus” there is marked increase in several “cardiovascular disorders including peripheral vascular disease, congestive heart failure, CAD and myocardial insufficiency” and a one to five fold increase in sudden demise. “Silent ischemia” is frequent in individuals with diabetes and a “thorough cardiac assessment is indicated in patients undergoing major surgery”.

Infections:

“Individuals with diabetes mellitus exhibit a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with

hyperglycemia as well as diminished vascularisation secondary to long standing diabetes."

Antidiabetic drugs:

Classification of antidiabetic drugs[41]

A.Enhance insulin secretion

1. Sulfonylureas:

- First generation-e.g. Tolbutamide
- Second generation-e.g. Glibenclamide, Glipizide, Glimepiride

2. Meglitinide analogues : Repaglinide, Nateglinide

3. Glucagon like peptide-1 (GLP-1) receptor agonists : Exenatide, Liraglutide

4. Dipeptidyl peptidase-IV (DPP-IV) inhibitors : Sitagliptin, Vildagliptin

B.Overcome insulin resistance

- Biguanides: Metformin
- Thiazolidinediones: Pioglitazone

C.Miscellaneous antidiabetic drugs

- Alpha-glucosidase inhibitors: Acarbose, Voglibose
- Amylin analogs: Pramlintide
- Dopamine-D2 receptor agonist : Bromocriptin

- Sodium glucose cotransport-2 (SGLT-2) inhibitor : Dapagliflozin

TREATMENT:

General Approach to Treatment:

Proper consideration requires goal setting for "glycemia, blood pressure, and lipid levels, regular monitoring for complications, dietary and exercise modifications, meditations, appropriate self-monitored blood glucose (SMBG)", and research facility evaluation of the previously stated parameters.

Glycemic Goals Stinting and the Hemoglobin A1C:

Controlled clinical trials give abundant proof that "glycemic control" is principal in diminishing "microvascular" complication in "both type 1 DM[42] and type 2 DM."[43] "HbA1c" estimations are the best standard for long term "glycemic control" for the past 2 to 3 months.[49] "HbA1c" focus of <7% is suitable, and lower value should be focused on if hypoglycemia and/or weight increase can be prevented.

Monitoring Complications: [42]

The ADA suggests observation of complications at the time of diagnosing DM. Current proposals support yearly eye examinations in "type 2 DM", Less number of testing (each 2 to 3 years) can be executed by an Ophthalmologist. The feet should be analyzed and blood pressure evaluated at every visit. Urine test for microalbumin once yearly is suggested. Yearly testing for lipid variations is prescribed.

Self Monitoring Of Blood Glucose (SMBG):

"The discovery of SMBG in the 1980s helped in the treatment of DM, empowering patients to know their blood glucose concentration effectively and easily.[43] The optimal frequency of SMBG for patients with type 2 DM is uncertain. Frequency of monitoring in type 2 DM should be adequate to facilitate reaching glucose goals. The role of SMBG in enhancing glycemic control in type 2 DM patients however has demonstrated to reduce the HbA1c ~0.4%."[44]

Non pharmacological Therapy:

Diet:

"Medical Nutrition Therapy" is suggested for all persons with DM.[45] Paramount for all medicinal sustenance treatment is the fulfillment of ideal metabolic results and the avoidance and treatment of complications. For people with type 1 DM, the emphasis is on managing insulin dosage with a balanced diet regimen to accomplish and maintain a healthy body weight. A diet that is moderate in starches and low in fat (<7% of aggregate calories), is advocated.[46]

Patients should be educated about the Carbohydrate that is taken in and the control of glucose. In order to reduce weight the amount of calories taken in should be greatly restricted. The cultural behavior and the financial condition of the patient should be taken into consideration when planning a "healthy diabetic diet". Since most of the patients with Type 2 DM are obese, between meal snacks are best avoided if treatment with drugs are sufficient.

Physical Activity:

Most patients with DM can profit by increasing their physical activity. "Aerobic exercise improves insulin resistance and glycemic control in the vast majority of people, and lessens cardiovascular risk factors, contributes to weight loss or maintenance, and improves well-being."

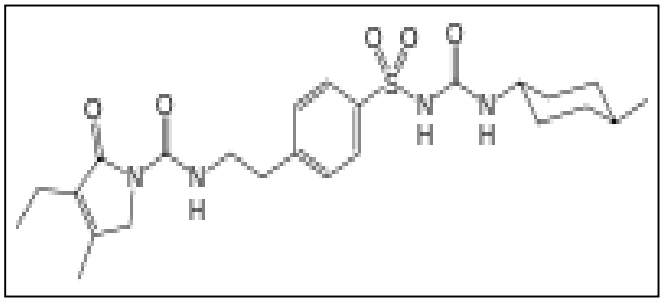
Pharmacological Therapy:

At present, six classes of orally active drugs are approved for the treatment of type 2 diabetes:- glucosidase inhibitors, biguanides, meglitinides, peroxisome proliferator-initiated receptor B-agonists (which are likewise ordinarily recognized as thiazolidinediones [TZDs] or glitazones), DPP-IV inhibitors, and sulfonylureas.

"Oral antidiabetic drugs are grouped regularly by their glucose-lowering mechanism of action." Biguanides and TZDs are frequently categorized as insulin sensitizers in light of their capacity to diminish insulin resistance. Sulfonylureas and meglitinides are regularly categorized as insulin secretagogues on the grounds that they increase endogenous insulin discharge. New alternatives for execution of insulin therapy are presently accessible.

The following drugs were used in the study:

GLIMEPRIDE:[47]



3-ethyl-4-methyl-*N*-(4-[*N*-((1*r*,4*r*)-4-methylcyclohexylcarbamoyl)sulfamoyl]phenethyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxamide

Glimepiride is a medium-to long-acting sulfonylurea antidiabetic drug. It is in some cases delegated either the first third-generation sulfonylurea,or as second-generation. Its compound structure is demonstrated in figure underneath.

Medical uses:

It is used in the treatment of type II diabetes.

Mechanism of action:

"The drug works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells. This inhibition causes cell membrane depolarization opening voltage-dependent calcium channel. This results in an increase in intracellular calcium in the pancreatic beta cell and subsequent stimulation of insulin release."

Pharmacokinetics:

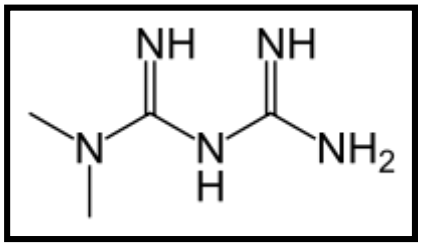
"The gastrointestinal absorption is complete, with no interference from meals. Significant absorption can occur within 1 hour, and distribution is throughout the body, 99.5% bound to plasma protein. Metabolism is by oxidative biotransformation. Excretion in the urine is 65%, and the remainder is excreted in the faeces."

Side effects and contraindications:

The adverse impacts incorporate gastrointestinal tract distrubances, rare hypersensitivity and occasional blood dyscrasias like thrombocytopenia, leukopenia, and hemolytic anemia. In the few weeks of treatment, the danger of hypoglycemia is enhanced. Consuming Liquor and exposure to sunlight ought to be limited on the grounds that they can aggravate reactions.

Its use is contraindicated in patients with hypersensitivity to glimepiride and during pregnancy.

METFORMIN: [48,49,50]



N,N-dimethylimidodicarbonimidic diamide

Metformin is an oral antidiabetic medication in the biguanide class. It is the first-line medication of option for the treatment of type 2 diabetes, specifically, in overweight individuals and those with a normally functioning kidney. Metformin is the main antidiabetic medication that has been definitively demonstrated to keep the cardiovascular obstacles of diabetes in check. It was discovered in the 1920s and in 1957, French doctor Jean Sterne made available the first clinical trial of metformin as a treatment for diabetes. It was presented in the United Kingdom in 1958.

Metformin is currently accepted to be the most broadly recommended antidiabetic medication on the planet. Its compound structure demonstrated in above figure.

Mechanism of action:

Metformin improves hyperglycemia principally by decreasing glucose production by the liver (hepatic gluconeogenesis). The "average" individual with type 2 diabetes has three times the “normal rate of gluconeogenesis”; metformin treatment lessens this by more than 33%.

Metformin initiates AMP-activated protein kinase (AMPK), a compound that assumes an important role in insulin signaling, energy balance of the entire body, and the metabolism of glucose and fats; “activation of AMPK” is needed for metformin's inhibitory impact on the generation of glucose by liver cells. The

mechanism by which biguanides enhance the activity of AMPK is not certain. On the other hand, studies suggest that Metformin enhances the amount of cytosolic AMP.

"In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake, fatty acid oxidation increase and decreases the absorption of glucose from the GI tract. Increased peripheral utilization of glucose may be due to increased insulin binding to its receptors. AMPK probably plays a role, as metformin administration increases AMPK activity in skeletal muscle."

Medical Uses:

Metformin is essentially utilized for type 2 diabetes. It is additionally utilized as a part of polycystic ovary disorder (PCOD), Nonalcoholic Fatty liver Diseases (NAFLD) and precocious puberty.

Pharmacokinetics:

Metformin has an oral bioavailability of 50–60% under fasting conditions, and slowly absorbs. Metformin is not metabolized. It is cleared from the body by tubular secretion and eliminated unaltered in the urine; metformin is imperceptible in blood plasma in 24 hours of a solitary oral measurement. The normal elimination half-life in plasma is 6.2 hours.

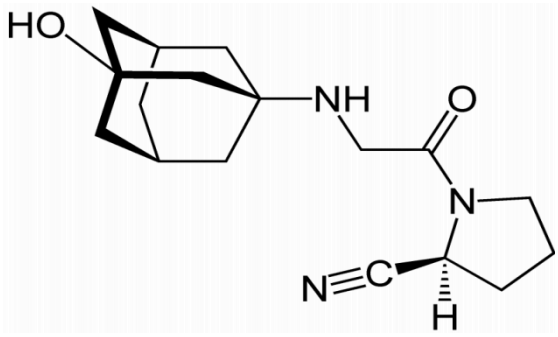
Adverse effects:

The most widely recognized unfavorable impact of metformin is gastrointestinal distress, including loose bowels, spasms and sickness. Metformin is more usually connected with gastrointestinal symptoms than most other antidiabetic medications.

The most genuine potential effect of metformin therapy is lactic acidosis; this consequences is uncommon, and the greater part of these cases appear to be identified with comorbid conditions, for example, altered liver or kidney function, as opposed to metformin itself.

Metformin has likewise been accounted to diminish the blood levels of thyroid hormone in individuals with hypothyroidism and in men, testosterone.

VILDAGLIPTIN: [51,52]



(*S*)-1-[*N*-(3-hydroxy-1-adamantyl) glycyl]pyrrolidine-2-carbonitrile

“Vildagliptin is a dipeptidyl peptidase-4 inhibitor. Its chemical structure is shown in figure below. Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in insulin secretion and blood glucose control regulation.”

Inhibitors of DPP-4 have long been sought as tools to elucidate the functional significance of the enzyme.The primary inhibitors were portrayed in the late 1980s and 1990s. Every inhibitor was vital to build up an early structure movement relationship (SAR) for resulting examination. It ought to be noticed that the inhibitors fall into two fundamental classes, those that interact covalent with DPP-4 and those that don't.

DPP-4 is a dipeptidase that specifically binds substrates that contain proline at the P1-position, accordingly numerous “DPP-4 inhibitors have 5-membered heterocyclic” rings that “mimic proline” e.g. “pyrrolidine, cyanopyrrolidine, thiazolidine and cyanothiazolidine.” These usually shape covalent bonds to the catalytic residue Ser630. DPP-4 inhibitors inhibit DPP-4 and prolongs the duration of GLP-1and GIP action, bringing about lower blood glucose level.

Adverse effects of Vildagliptin:

In clinical trials, adverse effects were common with vildagliptin (whether utilized alone or with metformin or pioglitazone) from rare nausea and flu-like

illness. There have been a few postmarketing reports of pancreatitis (some deadly) in individuals treated with vildagliptin, and the U.S. package insert carries a warning to this impact.

Studies related to effect of Metformin-Glimepiride and Metformin-Vildagliptin combined effect on Various Parameters:

Ohira M et al[53] led a study to look at the impacts of expanding the measurement of metformin and extra sitagliptin on MDA-LDL in type 2 diabetes patients. Seventy patients with type 2 diabetes, deficiently controlled in spite of on-running treatment with metformin 500 mg/day, were selected in this randomized controlled trial and changes in metabolic parameters including MDA-LDL were assessed. MDA-LDL levels (mean ± S.E.) diminished altogether with expanding the dosage of metformin (from 94.40 ± 6.35 to 77.83 ± 4.74 U/L, $P < 0.005$). These outcomes recommend that expanding the dosage of metformin enhances serum MDA-LDL levels in type 2 diabetes mellitus

Hadeel Delman et al in the study thought about the impacts of an insulin sensitizer, metformin, with an insulin secretagogue, glimepiride, on blood glucose level and lipid profile in recently analyzed type 2 diabetes. The randomized study was completed on 50 recently analyzed type 2 diabetic patients and 20 solid subjects. Patients were haphazardly isolated into three gatherings and alloted for treatment with either metformin or glimepiride or both for 12 weeks. Following 12 weeks, FBG and HbA1c altogether diminished in

every treated gathering. The level of aggregate cholesterol (TC) and low-thickness lipoprotein cholesterol (LDL-c) were fundamentally diminished, though high-thickness lipoprotein (HDL-c) was expanded notably just in metformin regarded gathering as mono-treatment. Metformin enhance lipid profile when utilized as a part of type 2 diabetic patients and lessen the danger of cardiovascular entanglements.

Md. Akram Minhaj and Md. Waris pointed the study to assess the impact of metformin in mix with Glimepiride in patient with type 2 Diabetes Mellitus. Patients with Glycosylated Hemoglobin more than 6.5% were incorporated in the study. 30 creature in five gathering were haphazardly alloted for treatment in light of metformin and glimepiride in a measurement of 200 mg/kg and 17.5 mg/kg for 21 weeks. The examinations were directed between these five gatherings for HbA1C, FPG, PPG and lipid profile. On week 21, the critical decreases in HbA1c were found in medication treated gatherings yet the patients treated with metformin and glimepiride brought about fundamentally more prominent diminishments in HbA1C. Additionally the more noteworthy huge decreases were seen if there should arise an occurrence of FPG, aggregate cholesterol, serum triglyceride and LDL cholesterol in patient with metformin and glimepiride treated gathering.

Weitgasser R et al54 led open, uncontrolled reconnaissance study to analyze the adequacy and security of glimepiride in patients with Type 2 diabetes. An aggregate of 1770 patients were enlisted in the study and 284 patients were chosen for postliminary. Patients got 0.5 to >4 mg glimepiride once every day for a long time. HbA(1c) was lessened from 8.4% at benchmark to 7.1% following 4 months and 6.9% following 1 and 1.5 years. Treatment with glimepiride likewise brought about critical and stable weight reduction in respect to gauge, except for patients with a body mass record of <25 kg/m(2).

Charpentier G et al55 directed a randomized, twofold visually impaired, twofold sham, parallel gathering multicentre study to look at the impact of glimepiride in mix with metformin and monotherapy of every medication on glycemic control in Type 2 diabetic patients. Type 2 diabetic patients matured 35-70 years deficiently controlled by metformin monotherapy 2550 mg every day for no less than 4 weeks were randomized to either metformin, glimepiride or metformin and glimepiride. 372 patients matured 56 +/ - 8 years were dealt with for 5 months. Blend treatment was altogether more effective in controlling HbA1c, fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) than either glimepiride or metformin alone. The frequency of symptomatic hypoglycaemia was higher in the blend bunch than in either monotherapy bunch (P = 0.039).

Ferrannini E. et al56 analyzed the adequacy and wellbeing of vildagliptin versus glimepiride as extra treatment to metformin in patients with type 2 diabetes mellitus in a 52-week between time examination of a vast, randomized, twofold visually impaired, multicentre study. At the point when metformin alone neglects to keep up adequate glycaemic control, the expansion of vildagliptin gives tantamount viability to that of glimepiride following 52 weeks and presentations a positive unfriendly impact profile, with no weight increase and a noteworthy diminishment in hypoglycaemia contrasted and glimepiride.

V.Lukashevich et al evaluated the adequacy and security of vildagliptin as extra treatment to metformin in addition to glimepiride mix in patients with type 2 diabetes mellitus who had insufficient glycaemic control. Following 24 weeks, the balanced mean change in hemoglobin A1c (HbA1c) was −1.01% with vildagliptin and −0.25% with placebo, with a between-treatment distinction of −0.76% ($p < 0.001$). Altogether more patients on vildagliptin accomplished the HbA1c target $p< 0.001$. The distinction in fasting plasma glucose decrease in the middle of vildagliptin and placebo was −1.13 mmol/l ($p < 0.001$). In subgroup of patients with benchmark HbA1c ≤8%, vildagliptin diminished HbA1c by 0.74% from pattern 7.82% with altogether more patients accomplishing the HbA1c target

Bosi E. et al thought about the adequacy and security of vildagliptin and metformin beginning mix treatment with individual mono treatments in treatment-guileless patients with type 2 diabetes mellitus (T2DM). In treatment-gullible patients, blends of vildagliptin and both high-measurement and low-dosage metformin give better viability than monotherapy medications with an equivalent general bearableness profile and okay of hypoglycaemia. The potential measurements saving impact of adding vildagliptin to low-dosage metformin in inclination to the up-titration of metformin may permit patients to accomplish equal or unrivaled HbA(1c) bringing down without the GI averageness issues connected with higher measurements of metformin.

Bosi E. et al assessed the adequacy and wellbeing of vildagliptin, another dipeptidyl peptidase-4 inhibitor, added to metformin amid 24 weeks of treatment in patients with type 2 diabetes. Vildagliptin is very much endured and delivers clinically significant, measurements related reductions in HbA1C and FPG as extra treatment in patients with type 2 diabetes insufficiently controlled by metformin.

Goodman M. et al57 assessed the adequacy and security of vildagliptin added to metformin in patients with type 2 diabetes mellitus. A multicentre, twofold visually impaired, randomized, placebo-controlled, 24-week study in patients insufficiently controlled with metformin was planned. Change from

pattern to study endpoint in balanced mean (SE) HbA(1c) enhanced fundamentally with vildagliptin AM dosing (- 0.66 [0.11] versus 0.17% [0.11] with placebo; p <0.001). Subgroup investigations uncovered that HbA(1c) lessening from standard was most prominent in those patients who had the most elevated pattern HbA1C.

"Jie Hong et al[73] conducted a study with an objective to compare the long-term effects of glipizide and metformin on the major cardiovascular events in type 2 diabetic patients. The study was a multicenter, randomized, double blind, placebo-controlled clinical trial. A total of 304 type 2 diabetic patients with CAD, mean age of 63.3 years were enrolled. Participants were randomly assigned to receive either glipizide (30mg daily) or metformin (1.5 g daily) for 3 years. The results concluded that metformin achieved a significant decrease in the level of glycated hemoglobin (7%). "

"Pravinkumar V. Ingle et al[74] conducted a study with an objective to appraise the effects of metformin in combination with glimepiride versus glibenclamide on lipid profile in Indian patients with type 2 diabetes mellitus. A total of 270 diabetic patients were selected for 26 weeks follow up on the basis of inclusion and exclusion criteria, having fasting plasma glucose ≥ 140 mg/dl and glycosylated hemoglobin (HbA_1c) ≥ 7%. Patients were received randomly metformin 1000 mg/day + glimepiride 2 mg/day or metformin 1000 mg/day + glibenclamide 10 mg/day for 26 weeks. The efficacy was measured by comparing the effects on lipid profile at the end of study period relative to the

baseline. All the 270 patients enrolled in the study receiving two varied combination treatment had the significant decrease in lipid profile by decreasing their LDL-C and same time increasing the HDL-C. Thus, study suggested that combination treatment with metformin plus glimepiride was more effective in improving lipid status of Indian type 2 diabetics than the metformin plus glibenclamide treatment. “

“R. D. Shimpi et al[76] aimed the present study to compare the effect of metformin in combination with Glimepiride and Glibenclamide in patient with type 2 Diabetes Mellitus.This was an open-label, randomized study carried out on glycaemic control in patient with type 2 Diabetes Mellitus. Patients with Glycosylated Hemoglobin more than 7% were included in the study. 31 patients were randomly assigned for treatment based on metformin-glibenclamide 1000/10 mg tablets or metformin-glimepiride1000/2mg for 12 weeks. The comparisons were conducted between these two groups for HbA1C, FPG, PPG and lipid profile. At week 12, the significant reductions in HbA1c were found in both groups but the patients treated with metformin and glimepiride resulted in significantly greater reductions in HbA1C than metformin and glibenclamide. Also the greater significant reductions were observed in case of FPG, total cholesterole, serum triglyceride and LDL cholesterole in patient with metformin-glimepiride group. “

"Aschner P et al[79] compared the efficacy and safety of monotherapy with sitagliptin and metformin in treatment-naïve patients with type 2 diabetes. In a double-blind study, 1050 treatment-naïve patients (i.e. not taking an antihyperglycaemic agent for > or =16 weeks prior to study entry) with type 2 diabetes and an HbA(1c) 6.5-9% were randomized (1:1) to treatment with once-daily sitagliptin 100 mg (N = 528) or twice-daily metformin 1000 mg (N = 522) for 24 weeks. Metformin was up-titrated from 500 to 2000 mg per day (or maximum tolerated daily dose > or =1000 mg) over a period of 5 weeks. From a mean baseline HbA(1c) of 7.2% in the population, HbA(1c) change from baseline was -0.43% with sitagliptin (n = 455) and -0.57% with metformin (n = 439). The between group difference (95% CI) was 0.14% (0.06, 0.21), thus confirming non-inferiority. Baseline HbA(1c) influenced treatment response, with larger reductions in HbA(1c) observed in patients with baseline HbA(1c)> or =8% in the sitagliptin (-1.13%; n = 74) and metformin (-1.24%; n = 73) groups. The proportions of patients at week 24 with HbA(1c) values at the goals of <7 or <6.5% were 69 and 34% with sitagliptin and 76 and 39% with metformin, respectively. Fasting plasma glucose changes from baseline were -11.5 mg/dL (-0.6 mmol/l) and -19.4 mg/dl (-1.1 mmol/l) with sitagliptin and metformin, respectively. The incidence of hypoglycaemia was 1.7% with sitagliptin and 3.3% with metformin (p = 0.116). In this monotherapy study, sitagliptin was non-inferior to metformin in improving HbA(1c) in treatment-naïve patients with type 2 diabetes."

"Wendy L Bennett et al[80] reviewed the benefits and harms of medications (metformin, second-generation sulfonylureas, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, and glucagon-like peptide-1 [GLP-1] receptor agonists), as monotherapy and in combination, for the treatment of adults with type 2 diabetes. Two reviewers independently screened titles to identify studies that assessed intermediate outcomes (e.g. hemoglobin A1c [HbA1c]), long-term clinical outcomes and harms in head-to-head monotherapy or combination therapy comparisons. The review included 140 randomized controlled trials and 26 observational studies. They graded evidence as low or insufficient for long-term clinical outcomes of all-cause mortality, cardiovascular disease, nephropathy, and neuropathy. Most medications lowered HbA1c on average by 1 absolute percentage point, but metformin was more efficacious than the DPP-4 inhibitors. Two-drug combinations had similar HbA1c reduction. Compared with metformin, thiazolidinediones and sulfonylureas had a more unfavorable effect on weight (mean difference of +2.6 kg). Metformin decreased low density lipoprotein cholesterol relative to pioglitazone, sulfonylureas, and DPP-4 inhibitors."

"Groop L et al[81] compared the effect of 6 months of insulin therapy twice daily with that of a combination of glibenclamide and metformin in 24 Type 2 diabetic subjects, who no longer responded to treatment with sulfonylureas. Both treatments resulted in an equivalent 30% improvement in mean daily blood

glucose ($p<0.001$), without significant effect on serum lipids. The combination of glibenclamide and metformin enhanced significantly total body glucose metabolism ($p<0.05$), predominantly by stimulating the non-oxidative pathway. “

“Gonzalez-Ortiz M et al[82] evaluated the efficacy and safety of glimepiride plus metformin in a single presentation, as combined therapy, in patients with type 2 diabetes mellitus (DM2) with secondary failure to glibenclamide. A randomized, double-blind, multicentric trial was carried out in 104 obese patients with DM2, fasting glucose > 140 mg/dL and glycated hemoglobin A1c (A1C) > 8%, in spite of treatment with glibenclamide at maximum doses and medical nutrition therapy for at least the 3 months previous to the study. Efficacy criteria were either a decrease in A1C of 1% or more, or a reduction in A1C of 7% or less. At the end of the study, the decrease in A1C concentration was -0.9 +/- 1.6% (CI 95%: -0.2 to -1.5) in the glimepiride group, -0.7 +/- 2.1% (CI 95%: 0.2 to -1.6) in the metformin group, and -1.3 +/- 1.8 mg/dL (CI 95%: -0.6 to -1.9) in the combined therapy group. The percentage of patients that showed a decrease in AIC of 1% or higher was 35.1, 21.2 and 47.0% in the glimepiride, in the metformin and in the combined therapy groups, respectively ($p < 0.001$). The percentage of patients with decreased AIC of 7% or less was 18.9, 9.0 and 23.5% in the glimepiride, in the metformin and in the combined therapy groups, respectively ($p = 0.01$). The combined use of glimepiride plus metformin in a single presentation for 3 months showed to be

efficacious and safe in patients with DM2 and secondary failure to glibenclamide“

“Filozof C. et al[83] conducted randomized, double-blind, active-controlled study to demonstrate non-inferiority of vildagliptin compared with gliclazide, as an add-on therapy, in patients with Type 2 diabetes inadequately controlled with metformin. In patients with Type 2 diabetes inadequately controlled with metformin, addition of vildagliptin provided similar HbA(1c) lowering efficacy compared with gliclazide after 52 weeks of treatment. Although both treatments were well tolerated, vildagliptin treated patients had fewer hypoglycaemic events and did not gain weight.”

“Gallwitz B. et al[84] aimed to compare a dipeptidyl peptidase-4 inhibitor (linagliptin) against a commonly used sulphonylurea (glimepiride). Reductions in adjusted mean HbA(1c) were similar in the linagliptin and glimepiride groups, meeting the predefined non-inferiority criterion of 0·35%. Fewer participants had hypoglycaemia or severe hypoglycaemia with linagliptin compared with glimepiride. Linagliptin was associated with significantly fewer cardiovascular events. The results of this long-term randomised active-controlled trial advance the clinical evidence and comparative effectiveness bases for treatment options available to patients with type 2 diabetes mellitus. The findings could improve decision making for clinical treatment when metformin alone is insufficient”

"Arechavaleta R. et al[85] conducted a study to evaluate the efficacy and safety of adding sitagliptin or glimepiride to the treatment regimen of patients with type 2 diabetes mellitus and inadequate glycaemic control on metformin monotherapy. In patients with type 2 diabetes and inadequate glycaemic control on metformin monotherapy, the addition of sitagliptin or glimepiride led to similar improvement in glycaemic control after 30 weeks. Sitagliptin was generally well tolerated. Compared to treatment with glimepiride, treatment with sitagliptin was associated with a lower risk of hypoglycaemia and with weight loss. "

"Hermansen K. et al[87] assessed the efficacy and safety of a 24 week treatment with sitagliptin, a highly selective once-daily oral dipeptidyl peptidase-4 (DPP-4) inhibitor, in patients with type 2 diabetes who had inadequate glycaemic control while on glimepiride alone or in combination with metformin. Sitagliptin 100 mg once daily significantly improved glycaemic control and beta-cell function in patients with type 2 diabetes who had inadequate glycaemic control with glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy and the observed degree of glycaemic improvement"

"Charbonnel B. et al[89] conducted a study on efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, added to ongoing metformin therapy, were assessed in patients with type 2 diabetes who had inadequate glycemic control with metformin alone. At week 24, sitagliptin treatment led to significant reductions compared with placebo in A1C (-0.65%), fasting plasma glucose, and 2-h postmeal glucose. Fasting insulin, fasting C-peptide, fasting proinsulin-to-insulin ratio, postmeal insulin and C-peptide areas under the curve (AUCs), postmeal insulin AUC-to-glucose AUC ratio, homeostasis model assessment of beta-cell function, and quantitative insulin sensitivity check index were significantly improved with sitagliptin relative to placebo. A significantly greater proportion of patients achieved an A1C <7% with sitagliptin (47.0%) than with placebo (18.3%). There was no increased risk of hypoglycemia or gastrointestinal adverse experiences with sitagliptin compared with placebo. Body weight decreased similarly with sitagliptin and placebo."

MATERIALS AND METHODS

Study Design:

A Prospective randomized controlled open label comparative study for a period of 12 weeks.

Source of Data:

Patients visiting the Medicine out-patient section at Karpaga Vinayaga Institute of Medical Sciences, Madhurantagam with type 2 diabetes mellitus.

Method of collection of data:

Sample Size:

The sample size had been estimated in consultation with a biostatistician based on previous year's case load and the sample size is 70 [35 in each arm].

Based on previous studies, in order to establish statistical significance for change in HbA1C and FBS/PPBS- it was required to study at least 35 patients in each arm at a probability α error of 5% and keeping power of study at 80%.

70 patients diagnosed with Type 2 diabetes mellitus attending medicine out-patient section were included in the study.

Inclusion criteria: -

1) Patients diagnosed with type 2 diabetes mellitus.
2) HbA1c levels between ≥ 7 and ≤10%.
3) Age ≥ 40 years and ≤ 80 years.

Exclusion criteria:

1) Patients diagnosed with Type 1 diabetes mellitus.
2) Those with known adverse reactions to Vildagliptin.
3) Cardiovascular diseases:
   - Severe hypertension
   - Any untoward Cardiac or cerebrovascular emergencies, that had happened previously.
4) Significant Gastrointestinal diseases like intestinal obstruction, malabsorption syndromes, irritable bowel syndrome, inflammatory bowel disease etc.
5) Serum creatinine more than 1.2 mgs/dl.
6) Those with raised Alanine Transaminase (ALT), Aspartate Transaminase (AST) ≥2 times normal.

7) Pregnancy and lactation.
8) Subject with any condition which, in the clinician's judgment, may render the subject not able to finish the study or which may represent a critical danger to the subject.
9) Concomitant medications with any other oral antidiabetic agents, chronic corticosteroids (oral or parenteral,>7 consecutive days of treatment) or any drugs which is known to alter the sugar levels are not permitted.

Timeframe:

The study was undertaken for the span of one year and 3 months(15 months from January 2014 to March 2015).

Investigations:

- FBS and PPBS at baseline, 6^{th} week and 12^{th} week.
- HbA1c, at baseline and at 12^{th} week.

Method:

70 patients diagnosed with type 2 DM, attending outpatient clinic were recruited after obtaining clearance from Ethical Review Board and taking written informed consent. A baseline demographic data (age, sex, weight, blood pressure, associated diseases, habits, and drug history) was collected at the time of recruitment.

HbA1c, FBS and PPBS were done at the time of recruitment. Patients was randomly assigned in (1:1) ratio after randomization to either of two groups (35 in each group), one group prescribed glimepiride(1mg) +metformin (500mg) twice daily half an hour before meals and other group vildagliptin(50mg)+ metformin(500mg) twice half an hour before meals. HbA1c, FBS, PPBS was repeated at the end of 3rd month.

Group A: Patients on glimepiride(1mg) +metformin (500mg)

Group B: Patients on vildagliptin(50mg)+ metformin(500mg)

In case of any emergencies, infections or surgery- patient was switched over to insulin momentarily and was shifted back to the regular treatment as per study protocol on complete recovery. However, those who develop complications or morbidity associated with hyperglycaemia was withdrawn from the study.

Also, patients with fasting sugars > 200 mg/dl and/or postprandial sugars > 300 mg/dl at the 6th week of study were also withdrawn from the study and treatment was given as per the American Diabetes Association [ADA] guidelines.

Primary efficacy outcome:

1. Reduction in HbA1c levels from baseline to 12th week.

2. Reduction in FBS/PPBS levels from baseline to 6th and 12th week.

Laboratory Investigation in Study Groups:

An informed consent from the patient was taken. Blood tests were gathered in fasting state and was examined for fasting blood glucose and glycated hemoglobin. Again blood sample was collected from the same patient 2 hrs after meal for post prandial sugar level estimation.

10ml of blood was drawn under aseptic safety measures from clinically analyzed instances of diabetes and partitioned into 3 test tubes, stamped as 1, 2 and 3.

1. Test tube 1 Contains 2 ml of blood with anticoagulant, which is utilized for estimation of FBS (Glucose oxidase strategy)

2. Test tube 2 contains entire blood that is utilized for estimation of glycated hemoglobin (Ion Exchange Resin strategy)

3. Test tube 3 contains 2 ml of blood which will be gathered with anticoagulant after 2 hrs of food, which is utilized for estimation of PPBS.

BLOOD SUGAR LEVEL :

FASTING BLOOD GLUCOSE [58]

FBS is directly proportional to the severity of diabetes mellitus and the most commonly used marker for DM. In general FBS levels greater than

126mg/dl over and over are indicative of diabetes mellitus, provided that drugs such as glucocorticoids are not being administered.

POSTPRANDIAL BLOOD GLUCOSE [58]

Two consecutive post prandial tests are recommended for diagnosis. Blood is drawn at 2 hrs after ingestion of the meal or glucose load. Two post prandial tests with glucose levels of 200 mg/dl or higher at 2 hours are indicative of diabetes.

GLYCATED HEMOGLOBLIN

It is one of the best record of long haul control of blood glucose level. At the point when there is hyperglycemia proteins in the body experience glycation. Glycation is a non enzymatic procedure where the glucose in the wake of entering RBC shapes a Schiff's base with N terminal amino gathering of protein by an aldimine linkage which changes to a ketamine linkage by an irreversible Amadori revision. It stays inside the erythrocytes for the duration of its life.

Normal level of glycated hemoglobin (HbA1c) is about 4-7%. Elevated glycated hemoglobin indicates poor control of diabetes mellitus. The danger of retinopathy and renal intricacies are proportionately expanded with raised glycated hemoglobin esteem and also with increase in age and duration of

diabetes mellitus. HbA1c level reveals mean glucose level over previous 8-10 weeks.

Ethics and Human Subjects Issues:

Ethical committee approval was taken to carry out the study. Diabetic nephropathy patients that come on outpatient basis and admitted patients were selected. Informed consent was taken from the patient.

Statistical analysis:

Quantitative data was summarized in terms of descriptive statistics like mean and standard deviation for patients who are treated for both the therapies.

In order to test for statistical significance in mean values, appropriate T test oblique non-parametric test was employed. Qualitative parameters between two groups were tested by employing Chi square test of significance, oblique non-parametric test to study before and after the treatment.

OBSERVATION AND RESULTS

Table 1) Distribution of subjects according to age:

Age Group	Group A (%)	Group B (%)	Total (%)
40-50	09 (12.86)	08 (11.43)	**17(24.29)**
50-60	13(18.57)	14(20.00)	**27(38.57)**
60-70	07(10.00)	06(8.57)	**13(18.57)**
70-80	06(8.57)	07(10.00)	**13(18.57)**
Total	35(50)	35(50)	**70(100)**
Mean age (Years)	**58.34 ±10.14**	**58.63 ±9.95**	**P= 0.90***

(* P>0.05 Not Significant)

In the above table it was observed that mean age among Group A and Group B subjects were 58.34 ±10.14 and 58.63 ±9.95 years respectively and does not show any statistical difference (P>0.05).

The number of subjects in age group 50-60 years were maximum i.e. 13 (18.57%) and 14 (20%) in Group A and Group B respectively.

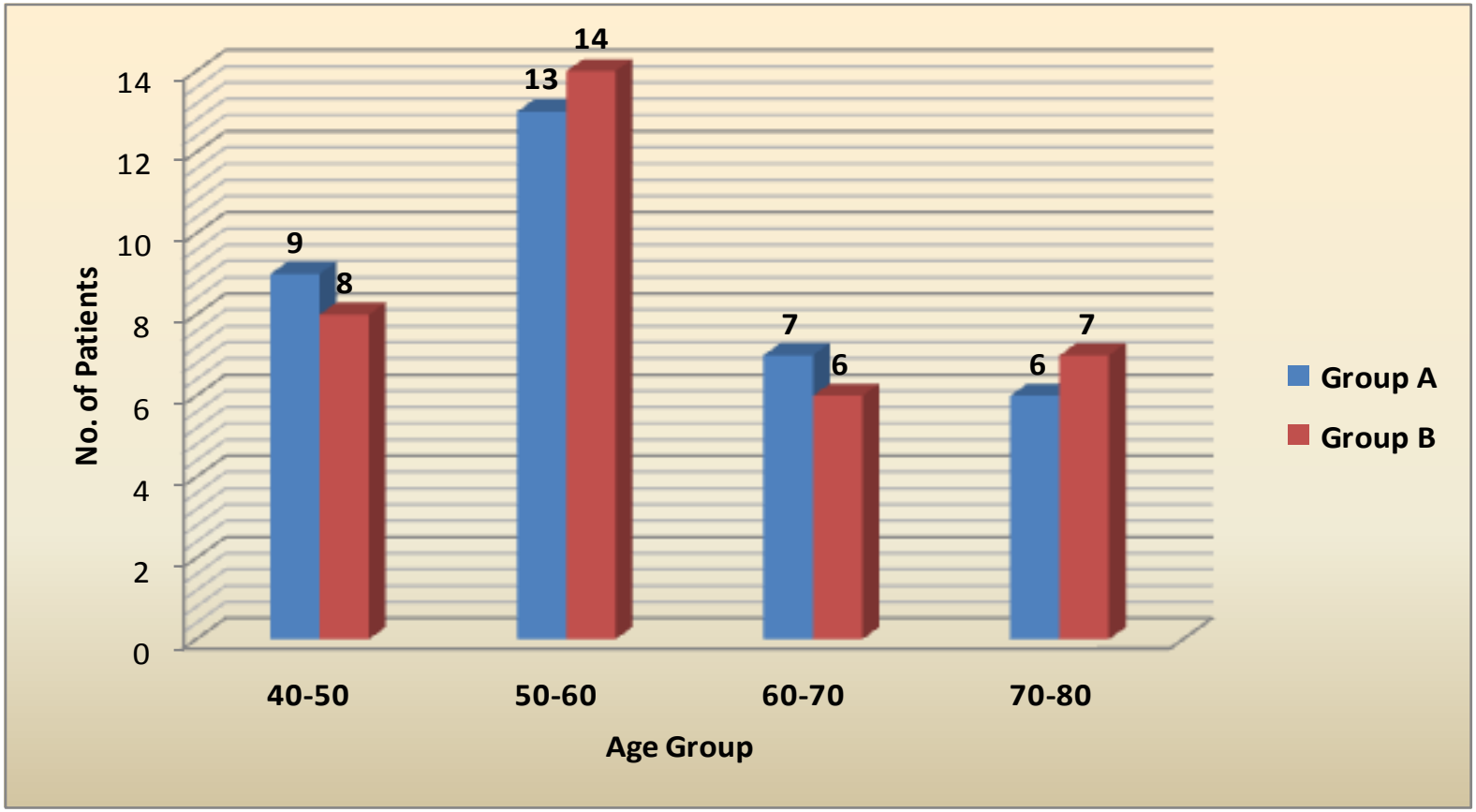


Figure 1: Distribution of subjects according to age

Table 2) Distribution of subjects according to sex:

Sex	Group A (%)	Group B (%)	Total (%)
Male	18 (25.71)	20 (28.57)	**38 (54.28)**
Female	17 (24.29)	15 (21.43)	**32 (45.72)**
Total	**35 (50)**	**35 (50)**	**70 (100)**

(X_2= 0.23 D.F=1; P=0.63 Not Significant)

In the study among 70 subjects, 38(54.28%) were male and 32 (45.72%) were females. The distribution of males and females in both the study groups were nearly similar with no statistical difference. (p>0.05).

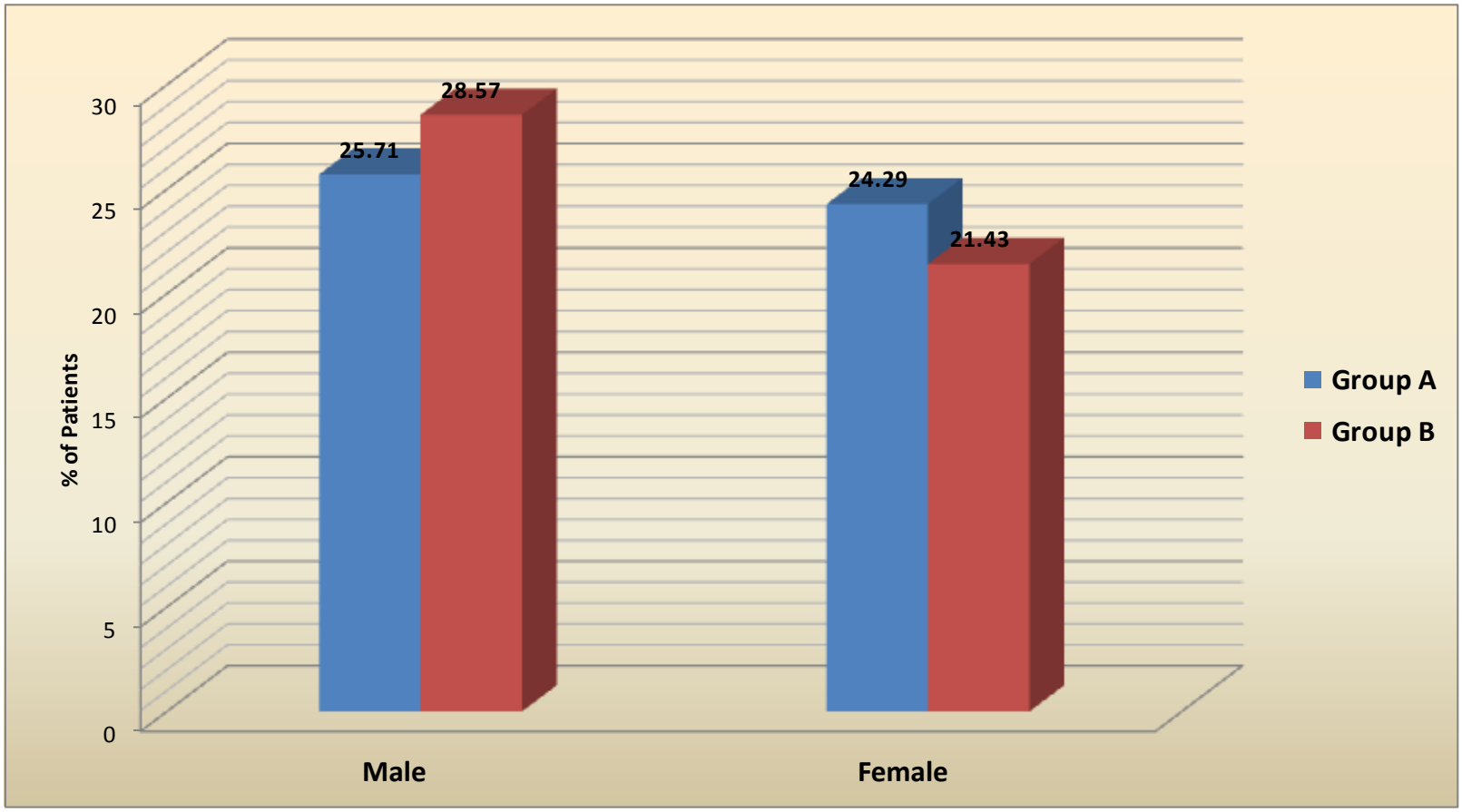


Figure 2: Sex distribution among subjects

Table 3) Distribution of subjects according to baseline blood sugar levels:

Variable	Group A	Group B	P value
FBS	179.06 ±32.56	174.03 ±19.19	0.43*
PPBS	270.86 ±43.82	277.94 ±28.41	0.42*
HbA1c	8.80 ±0.62	8.99 ± 0.37	0.12*

(* P>0.05 Statistically Not Significant)

In the study the mean fasting blood sugar levels at baseline (0 weeks) were Group A - 179.06 ±32.56 and Group B - 174.03 ±19.19 mg/dl . The contrast between two groups was not measurably huge. (P=0.43)

The mean post prandial blood sugar levels at baseline (0 weeks) were Group A - 270.86 ±43.82 and Group B - 277.94 ±28.41 mg/dl. The contrast between two groups was not measurably huge. (P=0.42)

The mean glycated haemoglobin (HbA1c) levels at baseline (0 weeks) were Group A - 8.80 ±0.62 and Group B - 8.99 ± 0.37. The contrast between two groups was not measurably huge. (P=0.12)

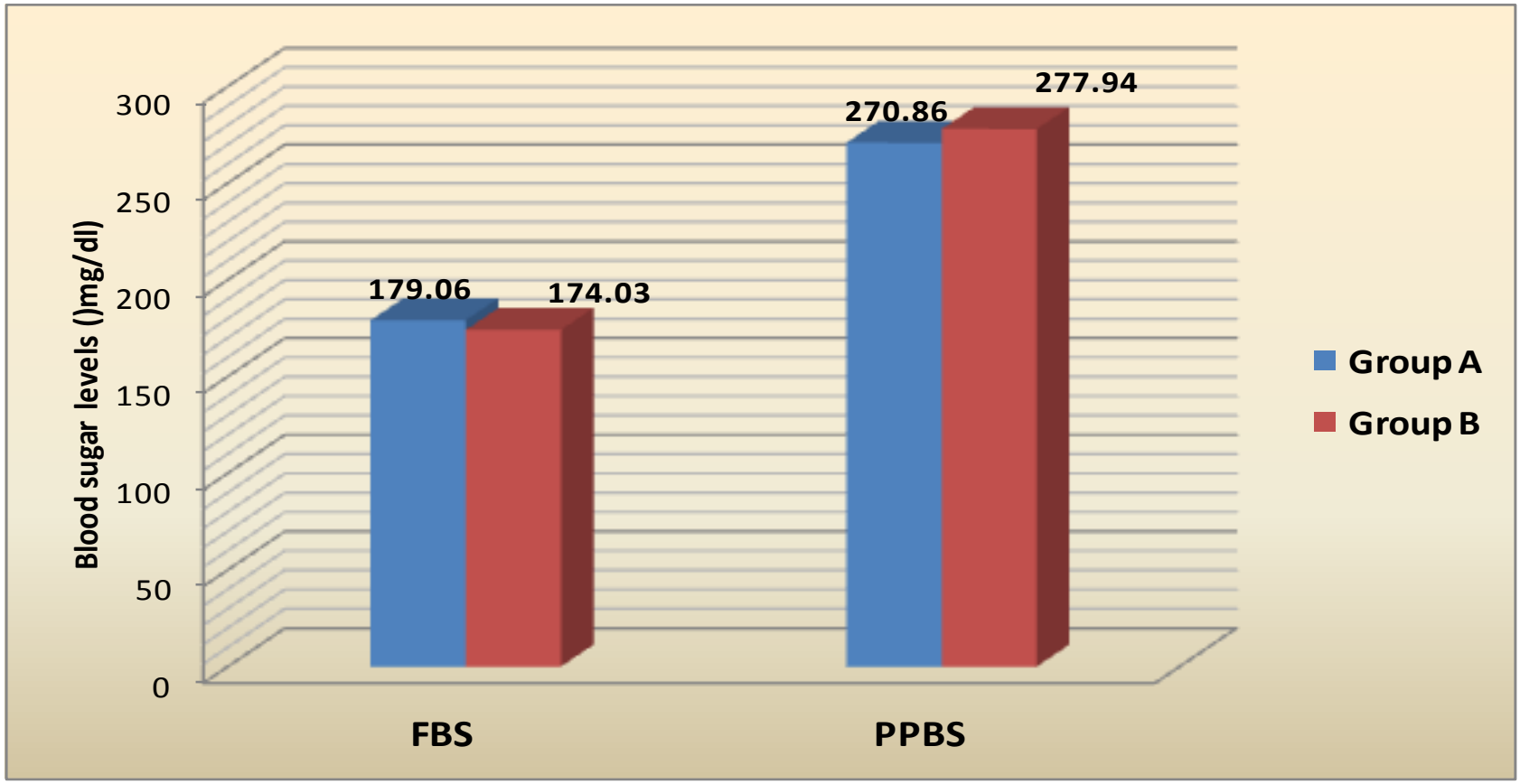


Figure 3: Distribution of subjects according to baseline blood sugar levels

Table 4) Effect of treatment on Fating Blood Sugar levels in study groups:

Time	Group A (Mean ±SD) (Glimepiride + metformin)	Group B (Mean ±SD) (Vildagliptin + metformin)	P value*
0 week	179.06 ±32.56	174.03 ±19.19	0.43
6 week	115.60±14.01	109.54±12.53	0.06
12 week	109.80±12.41	104.57±11.52	0.07
Change from baseline to 12 week (%)	-36.84 ±12.43	-39.33±8.54	0.33

(*P <0.05 Significant)

The mean fasting blood sugar levels at baseline (0 weeks) were Group A - 179.06 ±32.56 and Group B - 174.03 ±19.19 mg/dl. The fasting blood sugar levels at 6 weeks were Group A - 115.60±14.01 and Group B - 109.54±12.53 mg/dl.

Similarly, at 12 weeks mean fasting blood sugar levels were Group A - 109.80±12.41 and Group B - 104.57±11.52 mg/dl.

The change in percentage of fasting blood sugar at 12 weeks was Group A = -36.84% and Group B = -39.33% but nil statistical significance difference(P=0.33).

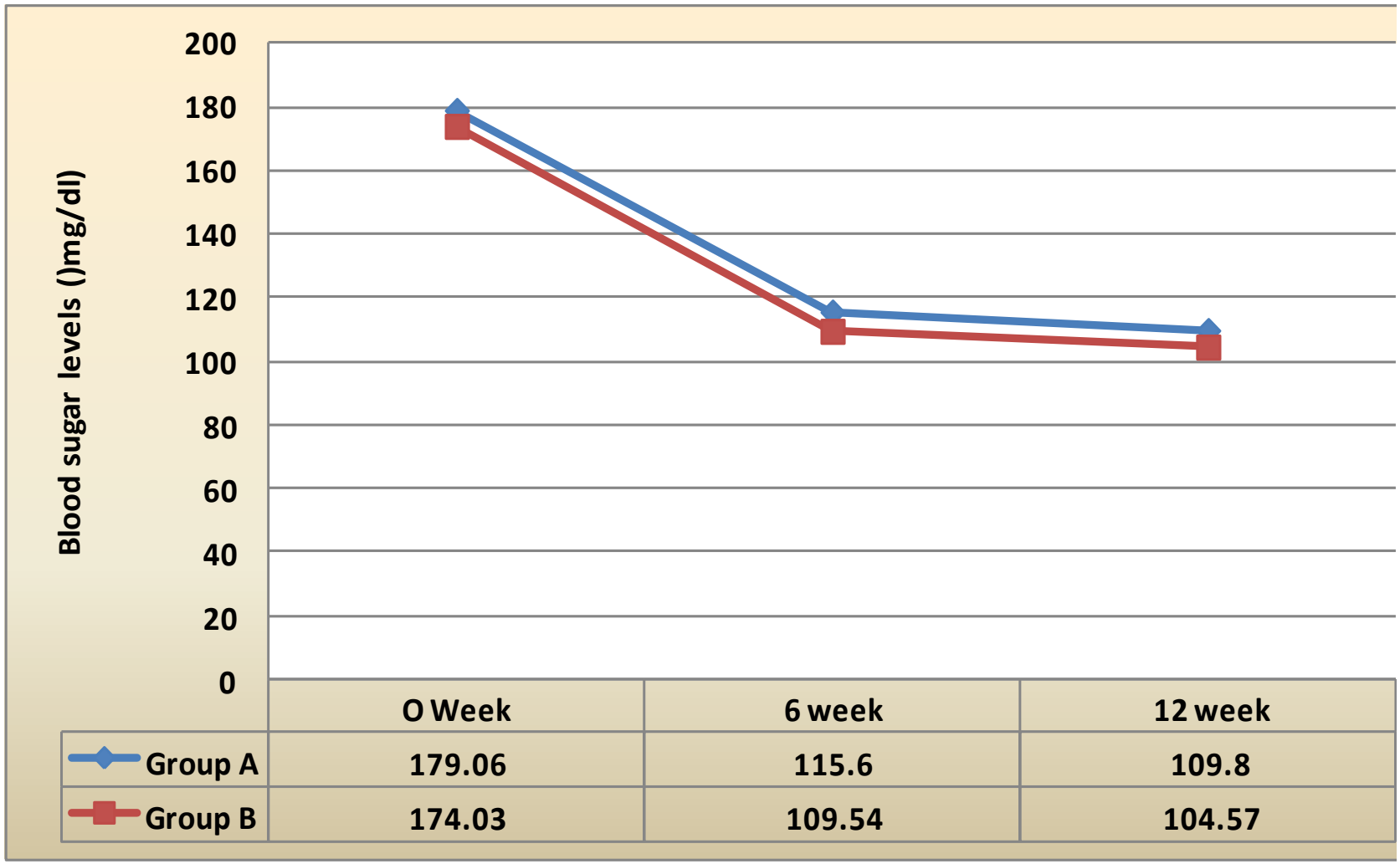


Figure 4 Effect of treatment on Fasting Blood Sugar levels in study groups

Table 5) Effect of treatment on Post prandial Blood Sugar levels in study groups

Time	Group A (Mean ±SD)	Group B (Mean ±SD)	P value
0 week	270.86 ±43.82	277.94 ±28.41	0.42
6 week	168.31±18.42	158.82 ±15.64	0.02*
12 week	159.03 ±15.99	154.45 ±13.91	0.21
Change from baseline to 12 week	-39.73±11.51	-43.88±7.42	0.07

(*P <0.05 Statistically Significant)

The mean Post prandial sugar levels at baseline (0 weeks) were Group A - 270.86 ±43.82 and Group B - 277.94 ±28.41 mg/dl. The Post prandial blood sugar levels at 6 weeks were Group A - 168.31±18.42 and Group B - 158.82 ±15.64mg/dl.

The difference between two groups shows statistical significance. (P=0.02). Similarly, at 12 weeks mean Post prandial blood sugar levels were Group A - 159.03 ±15.99 and Group B - 154.45 ±13.91 mg/dl.

The change in percentage of Post prandial blood sugar at 12 weeks was Group A = -39.73% and Group B = -43.88% but nil statistical significance difference. (P=0.07)

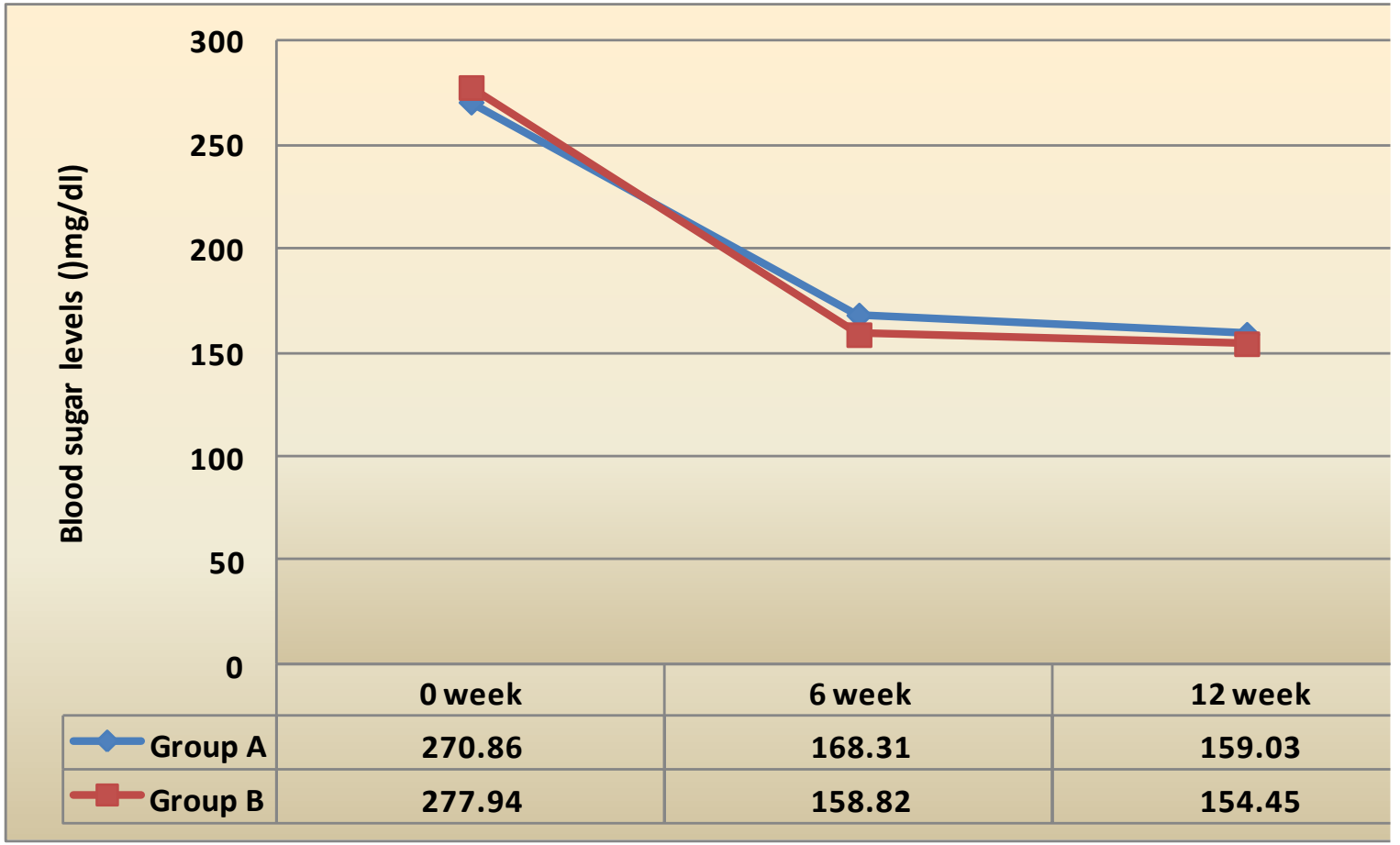


Figure 5 Effect of treatment on Post prandial Blood sugar levels in study group

Table 6) Effect of treatment on HbA1c levels in study groups:

Time	Group A	Group B	P value*
0 week	8.80 ±0.62	8.99 ±0.37	0.12
12 week	6.47±0.44	6.42±0.42	0.92
Change from baseline to 12 week	-26.06±7.47	-27.86±5.96	0.26

(*P <0.05 Statistically Significant)

The mean HbA1c levels at baseline (0 weeks) were Group A - 8.80 ±0.62 and Group B - 8.99 ±0.37. Similarly, at 12 weeks mean HbA1c levels were Group A - 6.47±0.44 and Group B - 6.42±0.42.

The change in percentage of HbA1c at 12 weeks was Group A = -26.06% and Group B = -27.86% but nil statistical significance difference. (P=0.26)

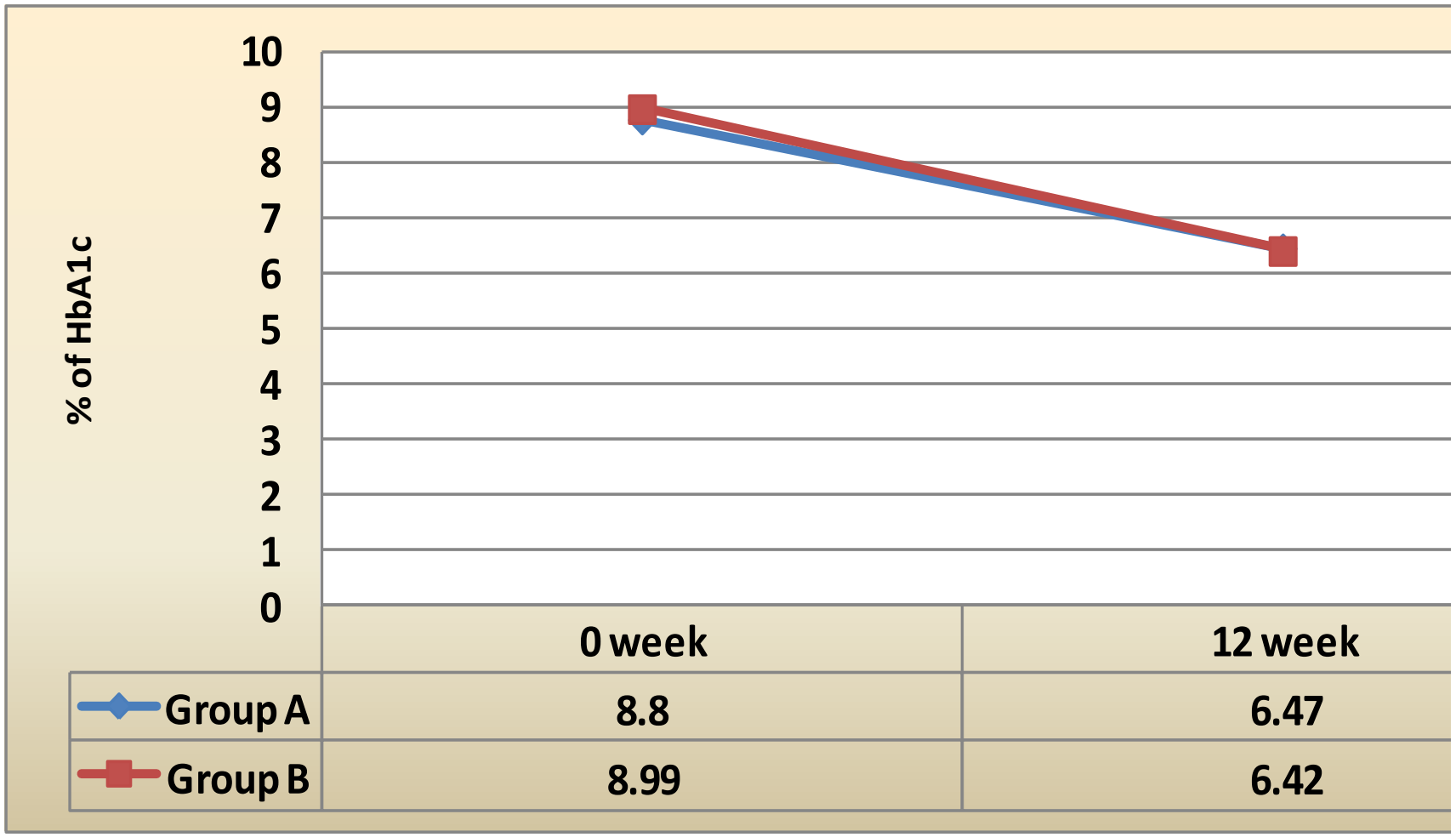


Figure 6: Effect of treatment on HbA1c levels in study groups

Table 7) Distribution of subjects according to levels of HbA1c:

HbA1c Levels	Group A (%)	Group B (%)	Total (%)
< 7	29 (41.43)	28 (40.00)	57 (81.43)
≥7	06 (8.57)	07 (10.00)	13 (18.57)
Total	35 (50)	35 (50)	70 (100)

(X_2= 0.07 D.F=1; P=0.75 Not Significant)

The HbA1c levels < 7 were achieved among 29 (41.43%) subjects in Group A as compared to 28 (40%) subjects in Group B.

The difference between HbA1c levels among study groups was not statistically significant. (P=0.75)

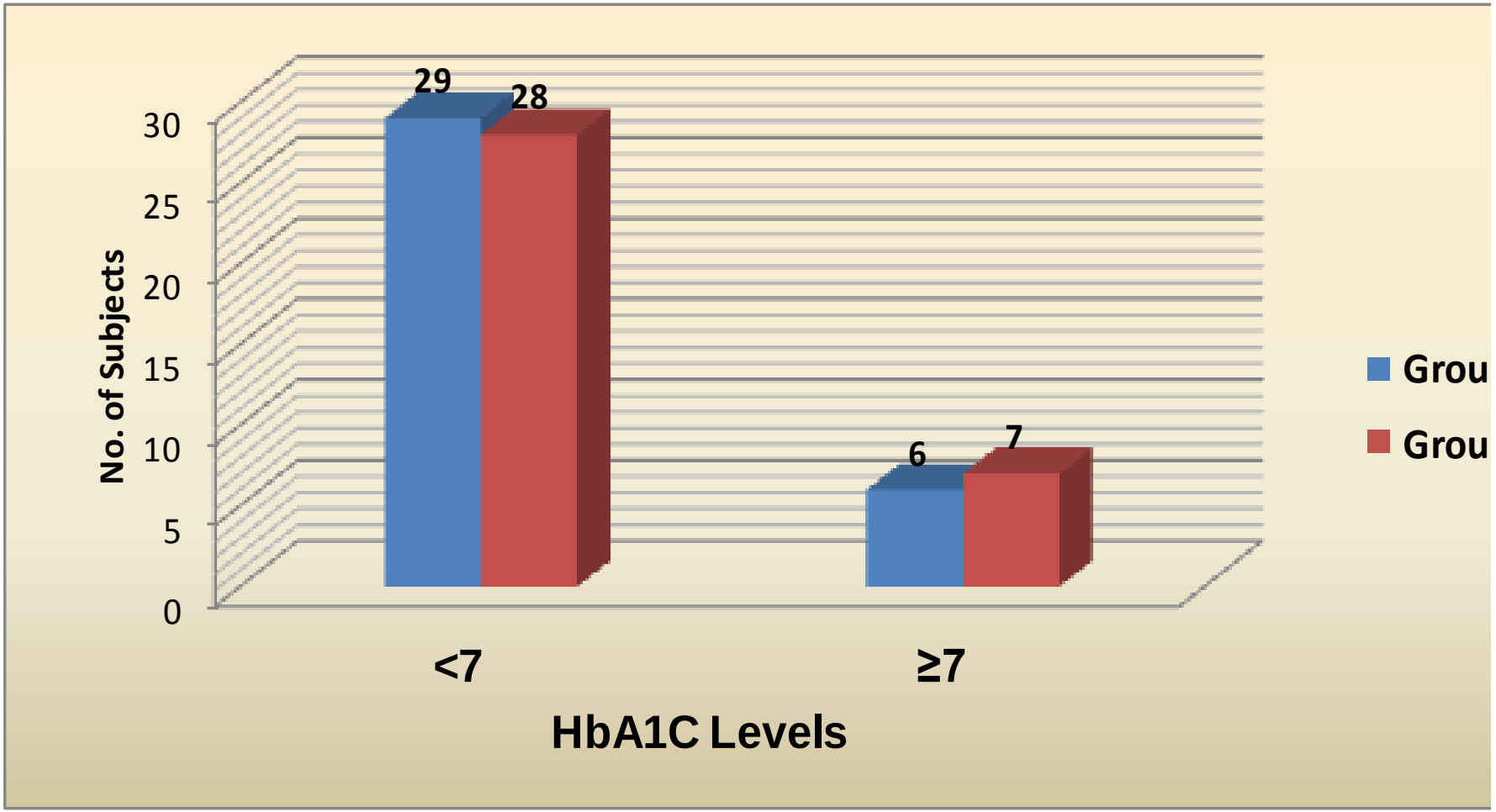


Figure 7 : Distribution of subjects according to levels of HbA1c

Table 8) Effect of treatment on BMI in study groups:

Time	Group A	Group B	P value*
0 week	24.96 ±4.65	24.09 ±3.98	0.40
12 weeks	25.20 ±4.51	23.56 ±3.80	0.10

(*P <0.05 Statistically Significant)

The mean BMI at baseline (0 weeks) were 24.96 ±4.65 and 24.09 ±3.98 in Group A and Group B respectively. Similarly, at 12 weeks mean BMI levels were Group A - 25.20 ±4.51 and Group B - 23.56 ±3.80.

It was observed that mean BMI in Group A subjects was slightly more than baseline while that in Group B subjects was slightly lower than baseline at 12 weeks but no statistically significant.

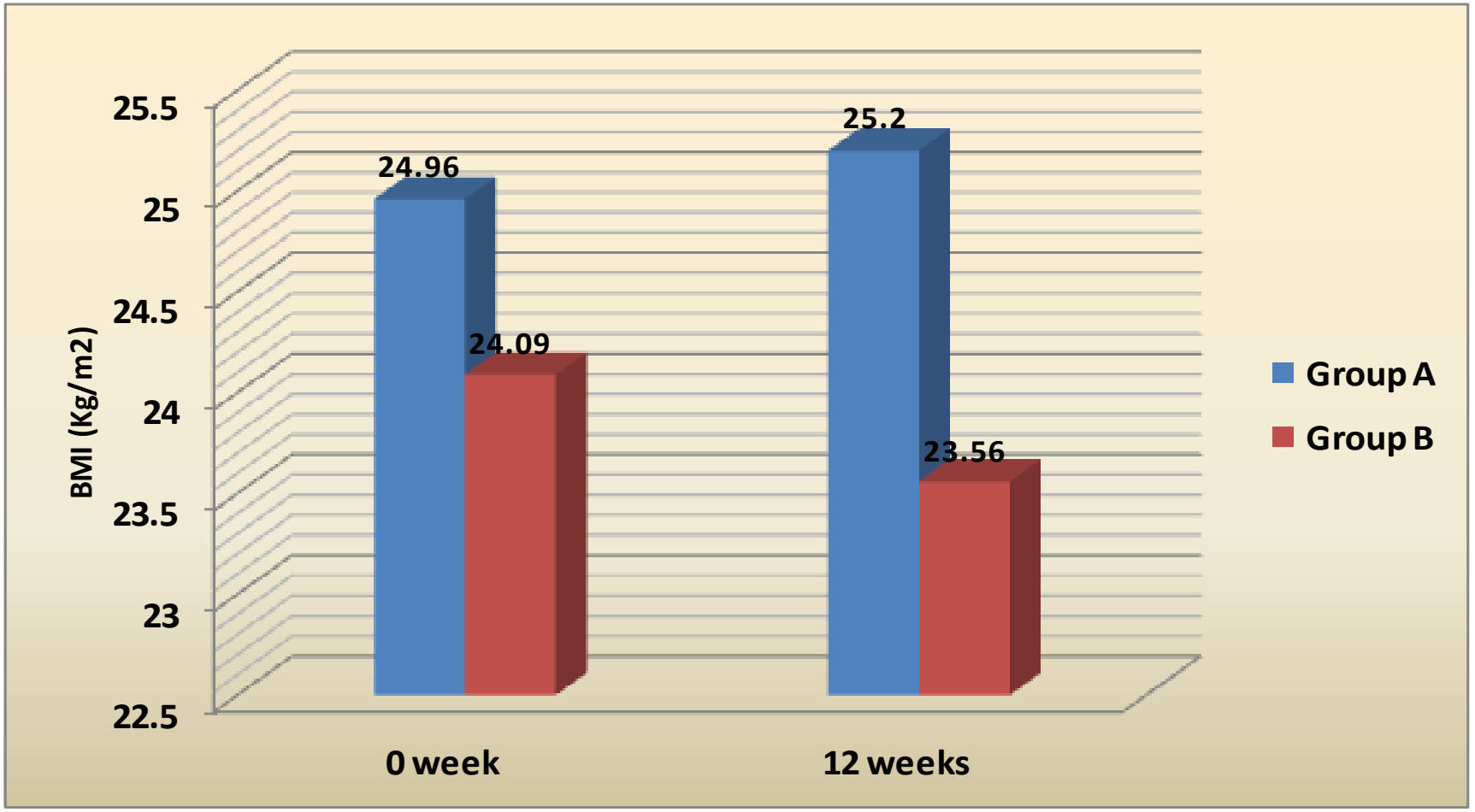


Figure 8: Effect of treatment on BMI in study group

Table 9: Distribution according to adverse effects among study groups:

Adverse Effects	Group A (n=35)	Group B(n=35)	P value*
Edema	4	3	0.50
Headache	3	5	0.35
Elevated liver enzymes	1	3	0.30
Symptomatic hypoglycemia	5	2	0.23
Abdominal discomfort	1	2	0.55
Diarrhea	2	8	0.04#
Chest discomfort & dyspnea	2	3	0.51
Others	3	5	0.35

(* P value calculated by Fisher Test and # P <0.05 significant)

The adverse effects in Group A subjects was maximum with related to hypoglycemia. 5 subjects suffered symptomatic hypoglycemia in Group A as contrasted to 2 subjects in Group B. Elevated liver enzymes was seen more in group B subjects along with diarrhoea which shows statistical significance.

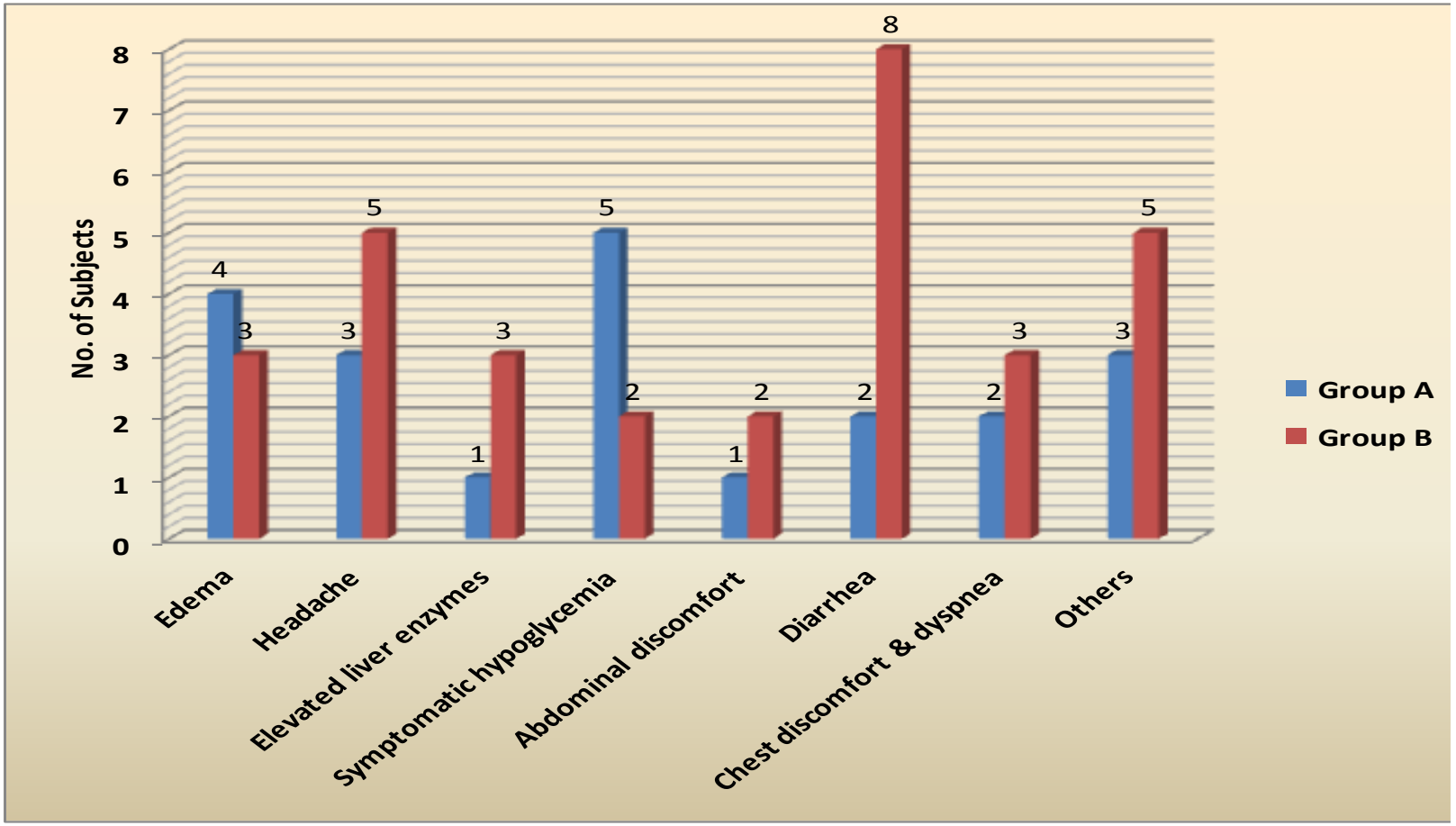


Figure 9:Distribution according to adverse effects among study groups.

DISCUSSION

The present study was completed to explore the viability and wellbeing of glimepiride-metformin and vildagliptin-metformin treatment in type 2 diabetic patients. The study was carried out in patients attending the medicine out-patient department at Karpaga Vinayaga Institute of Medical science and Research Centre, Madhurantakam.

General Characteristics among the study subjects:

In table no. 1, it was observed that mean age among Group A and Group B subjects were 58.34 ±10.14 and 58.63 ±9.95 years respectively and does not show any statistical difference (P>0.05). The number of subjects in age group 50-60 years were maximum i.e. 13 (18.57%) and 14 (20%) in Group A and Group B respectively.

In the study among 70 subjects, 38(54.28%) were male and 32 (45.72%) were females. The distribution of males and females in both the study groups were nearly similar with no statistical difference. (Table 2)

The mean body weight of Group A subjects was 63.68±8.89 kg and Group B subjects was 64.20 ±7.48 kgs with no statistical difference. (P=0.79).

The mean body mass index (BMI) of Group A subjects was 24.96 ±4.65 and Group B subjects was 24.09 ±3.98 with no statistical difference. (P=0.40)

Baseline (0 weeks) blood sugar levels and HbA1C among Study Subjects:

In the study the mean fasting blood sugar levels at baseline (0 weeks) were Group A - 179.06 ±32.56 and Group B - 174.03 ±19.19 mg/dl. The distinction between two groups was nil significant. (P=0.43)

The mean post prandial blood sugar levels at baseline (0 weeks) were Group A - 270.86 ±43.82 and Group B - 277.94 ±28.41 mg/dl. The distinction between two groups was nil significant. (P=0.42)

The mean glycated haemoglobin (HbA1c) levels at baseline (0 weeks) were Group A - 8.80 ±0.62 and Group B - 8.99 ± 0.37. The distinction between two groupss was nil significant. (P=0.12)

Efficacy of Glimepiride-metformin and Vildagliptin-metformin treatment in Study subjects:

The mean fasting blood sugar levels at baseline (0 weeks) were Group A - 179.06 ±32.56 and Group B - 174.03 ±19.19 mg/dl. The fasting blood sugar levels at 6 weeks were Group A - 115.60±14.01 and Group B - 109.54±12.53 mg/dl. Similarly, at 12 weeks mean fasting blood sugar levels were Group A - 109.80±12.41 and Group B - 104.57±11.52 mg/dl.

The change in percentage of fasting blood sugar at 12 weeks was Group A = -36.84% and Group B = -39.33% but nil statistical significance.(P=0.33)

The mean Post prandial sugar levels at baseline (0 weeks) were Group A - 270.86 ±43.82 and Group B - 277.94 ±28.41 mg/dl. The Post prandial blood sugar levels at 6 weeks were Group A - 168.31±18.42 and Group B - 158.82 ±15.64mg/dl.

The difference between two groups shows statistical significance. (P=0.02). Similarly, at 12 weeks mean Post prandial blood sugar levels were Group A - 159.03 ±15.99 and Group B - 154.45 ±13.91 mg/dl.

The change in percentage of Post prandial blood sugar at 12 weeks was Group A = -39.73% and Group B = -43.88% but nil statistical significance.(P=0.07)

The mean HbA1c levels at baseline (0 weeks) were Group A - 8.80 ±0.62 and Group B - 8.99 ±0.37. Similarly, at 12 weeks mean HbA1c levels were Group A - 6.47±0.44 and Group B - 6.42±0.42.

The change in percentage of HbA1c at 12 weeks was Group A = -26.06% and Group B = -27.86% but nil statistical significance.(P=0.26)

The HbA1c levels < 7 were achieved among 29 (41.43%) subjects in Group A as compared to 28 (40%) subjects in Group B.

The difference between HbA1c levels among study groups was statistically nil significant. (P=0.75)

The mean BMI at baseline (0 weeks) were Group A - 24.96 ±4.65 and Group B - 24.09 ±3.98. Similarly, at 12 weeks mean BMI levels were Group A - 25.20 ±4.51 and Group B - 23.56 ±3.80.

It was observed that mean BMI in Group A subjects was slightly more than baseline while that in Group B subjects was slightly lower than baseline at 12 weeks but no statistically significant.

The results in present study regarding plasma glucose and glycosylated hemoglobin (HbA1c) indicate that there was a successful improvement in plasma glucose levels and HbA1c after treatment courses of 6 and 12 weeks. The values were improved significantly after treatment with the drugs. However, this improvement was not enough to reach that of normal healthy individual values. In other words, there were partial improvements observed by these drugs.

Accordingly, and based on the comparison of the treatment we conclude that combination of metformin + vildagliptin significantly reduced the values of FPG, PPG and HbA1c after 3 months. This might due to the additive effect of these two drugs (metformin + vildagliptin).These results were in agreement with other study[56,59] results that also indicate effectiveness of additive effect of metformin and vildagliptin.

The incretin hormones assume a noteworthy part in glucose homeostasis by invigorating insulin discharge, stifling glucagons emission, hindering gastric clearing and lessening craving and sustenance intake.[60,61] Both incretin hormones

are quickly debased and expelled from flow by the protein dipeptidyl peptidase – 4 (DPP-4).[62,63] Therefore, there is significant enthusiasm for upgrading incretin activity for treatment of type 2 diabetes.

The blend treatment with Vildagliptin and metformin lower glucose through improvement of insulin discharge, concealment of glucagon emission, and insulin sharpening by fat tissue. The utilization of this mix in diabetes administration will give a more noteworthy level of glycosylated hemoglobin – bringing down than that seen with utilization of either medication as monotherapy.

Sulfonylurea drugs as a group had been on the market for a long time and were relatively low price. Sulfonylureas had the advantage of being quite effective in blood glucose lowering, with an almost instant onset of the effect after start of therapy. Drops in HbA1c of 1–2% can be expected as a mean, with the higher the baseline HbA1c, the bigger the drop.

The synergestic effects were seen when Sulfonylureas are combined with metformin, and the different mechanisms of action of these two agents – one stimulating insulin secretion, the other increasing insulin sensitivity – make them the obvious couple in the dual activity in type 2 diabetes.[65]

Vildagliptin should be used to its maximum potential, started early in the disease process to maintain and preserve beta cell function[66] and preferably used in combination with Metformin in order to achieve the maximum reduction in HbA1c.[67,68] All recent clinical trials hint to the benefit of the early use of vildagliptin, alone or in combination, of any antidiabetic medication.

Safety of Vildagliptin-metformin and Glimepiride-metformin treatment in Study subjects:

The adverse effects in Group A subjects was maximum with related to hypoglycemia. 5 subjects suffered symptomatic hypoglycemia in Group A as compared to 2 subjects in Group B. Elevated liver enzymes was seen more in group B subjects along with diarrhea which shows statistical significance.

In the present study Treatment with Vildagliptin emerge to be safe and well tolerated by most, as outlined in the previous sections. When administered in combination with other agents vildagliptin therapy appears unlikely to cause hypoglycemia and is generally weight-neutral. Other adverse effects noted to occur in clinical trials of DPP-4 inhibition have included increased reports of nasopharyngitis, upper respiratory infection, and headache – these were not likely to be severe or result in discontinuation of the medication.

The combination of Vildagliptin and metformin in type 2diabetes management has been shown in clinical trials to be effective in blood glucose lowering, with very low associated rates of hypoglycemia and no attenuation in the potential weight loss effects seen with metformin monotherapy.[70]

The main disadvantage of Glimepiride is the risk of hypoglycaemia, and increase weight which rises with advanced age, poor nutrition, alcohol consumption, liver or kidney disease and polypharmacy[70] and is higher than with other oral medications.[71]

SUMMARY

The present prospective randomized controlled open label comparative study was carried out to investigation to compare the efficacy and safety of vildagliptin - metformin and glimepiride –metformin treatment in type 2 diabetic patient. The study was carried out in patients attending medicine out-patient department of Karpaga Vinayaga Institute of Medical Sciences and Research Center, Madhuranthagam.

A total of 70 patients attending medicine out-patient department with type 2 diabetes mellitus who were newly diagnosed were included in the study.

The study revealed the following findings:

- The mean age among Group A and Group B subjects were 58.34 ±10.14 and 58.63 ±9.95 years respectively.
- The number of subjects in age group 50-60 years were maximum i.e. 13 (18.57%) and 14 (20%) in Group A and Group B respectively.
- Among 70 subjects, 38(54.28%) were male and 32 (45.72%) were females.
- The number of subjects with diabetes in group 1-3 years were more in Group A (17) as compared to Group B (13).

- The mean body weight of Group A subjects was 63.68±8.89 kg and Group B subjects was 64.20 ±7.48 kgs.
- The mean body mass index (BMI) of Group A subjects was 24.96 ±4.65 and Group B subjects was 24.09 ±3.98 with no statistical difference. (P=0.40)
- The mean fasting blood sugar levels at baseline (0 weeks) were 179.06 ±32.56 and 174.03 ±19.19 mg/dl in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.43)
- The mean post prandial blood sugar levels at baseline (0 weeks) were 270.86 ±43.82 and 277.94 ±28.41 mg/dl in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.42)
- The mean glycated haemoglobin (HbA1c) levels at baseline (0 weeks) were 8.80 ±0.62 and 8.99 ± 0.37in Group A and Group B respectively. The difference between two groups was not statistically significant. (P=0.12)
- The mean fasting blood sugar levels at baseline (0 weeks) were 179.06 ±32.56 and 174.03 ±19.19 mg/dl in Group A and Group B respectively.
- The fasting blood sugar levels at 6 weeks were 115.60±14.01and 109.54±12.53 mg/dl in Group A and Group B respectively.
- At 12 weeks mean fasting blood sugar levels were 109.80±12.41and 104.57±11.52 mg/dl in Group A and Group B respectively.

- The change in percentage of fasting blood sugar at 12 weeks was -36.84% and -39.33% in Group A and Group B respectively but no statistical significance different was found. (P=0.33)
- The mean Post prandial sugar levels at baseline (0 weeks) were 270.86 ±43.82 and 277.94 ±28.41 mg/dl in Group A and Group B respectively.
- The Post prandial blood sugar levels at 6 weeks were 168.31±18.42 and 158.82 ±15.64mg/dl in Group A and Group B respectively. The difference between two groups shows statistical significance. (P=0.02).
- At 12 weeks mean Post prandial blood sugar levels were 159.03 ±15.99 and 154.45 ±13.91 mg/dl in Group A and Group B respectively.
- The change in percentage of Post prandial blood sugar at 12 weeks was -39.73% and -43.88% in Group A and Group B respectively but no statistical significance different was found. (P=0.07)
- The mean HbA1c levels at baseline (0 weeks) were 8.80 ±0.62and 8.99 ±0.37 in Group A and Group B respectively.
- At 12 weeks mean HbA1c levels were 6.47±0.44 and 6.42±0.42 in Group A and Group B respectively.
- The change in percentage of HbA1c at 12 weeks was -26.06% and -27.86% in Group A and Group B respectively but no statistical significance different was found. (P=0.26)
- The HbA1c levels < 7 were achieved among 29 (41.43%) subjects in Group A as compared to 28 (40%) subjects in Group B. The difference

between HbA1c levels among study groups was not statistically significant. (P=0.75)

- It was observed that mean BMI in Group A subjects was slightly more than baseline while that in Group B subjects was slightly lower than baseline at 12 weeks but no statistically significant.
- The adverse effects in Group A subjects was maximum with related to hypoglycemia. 5 subjects suffered symptomatic hypoglycemia in Group A as compared to 2 subjects in Group B. Elevated liver enzymes was seen more in group B subjects along with diarrhea which shows statistical significance.

CONCLUSION

Thus from the present study we conclude that, the efficacy and tolerability of vildagliptin, was similar, with no significant differences, when used to treat type 2 diabetic patients with inadequate blood glucose control by dual combination of metformin and another traditional oral hypoglycemic agent (glimepiride).

Vildagliptin in combination with metformin also had good safety with low risk of hypoglycaemia and weight gain.

Annexure I

ABBREVEATIONS

ADA	American Diabetes Association
BMI	Body Mass Index
CVD	Cardio Vascular Diseases
DALY	Disability Adjusted Life Years
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
DM	Diabetes Mellitus
EASD	European Association for the Study of Diabetes
GDM	Gestational diabetes mellitus
GLP-1	Glucagon-like Peptide-1
GAD	Glutamic Acid Decarboxylase
ICA	Islet Cell Autoantibodies
OGTT	Oral Glucose Tolerance Test
ROS	Reactive Oxygen Species
RAAS	Renin Angiotensin Aldosterone System
WHO	World Health Organization (WHO)

Annexure II

KEY TO MASTERCHART

FBS=	Fasting Blood Sugar (mg/dl)
PPBS=	Post Prandial Blood Sugar (mg/dl)
HbA1C=	Glycated Haemoglobin (%)
BMI	Body Mass Index (kg/m^2)
ED	Edema
HD	Headache
EL	Elevated Liver Enzymes
HG	Hypoglycemia
D	Diarrhea

ANNEXURE: III

INFORMED CONSENT FORM

I, Mr/Mrs. _____, age _____ years residing at_____ hereby give my informed consent to participate in the project entitled, **"A COMPARATIVE STUDY ON THE SAFETY AND EFFICACY OF VILDAGLIPTIN - METFORMIN AND GLIMEPIRIDE-METFORMIN TREATMENT IN TYPE 2 DIABETIC PATIENT IN A TERTIARY CARE HOSPITAL"**

1. There is no compulsion on me to participate in this project and I am giving my free consent for it.
2. I have read and I have been explained the general information and purpose of the present project.
3. I know that, I can withdraw from the present project at any time.
4. Any data or analysis of this project will be purely used for scientific purpose and my name will be kept confidential except when required for any legal purpose.

Signature of Subject:

Signature of Principal Investigator:

Signature of Witness

Date:

Annexure IV

CASE RECORD FORM

Identification data

1. Name:
2. Sex: Male / Female
3. Age: _____(yrs) Date of Birth: _____
4. Caste/ Religion:_____
5. Address :- _____

Present Illness History:

Past History:

Family History:

Nutritional history :- Type of diet :- Mix / Vegetarian

Health checkup

General examination :-

1. General appearance:- Normal built / Thin Built / over weight
2. Pulse rate :-
3. Respiratory rate :
4. Edema over body:- present / absent
5. Any significant sign: specify _____

Systemic examination:-

1. CNS
2. CVS
3. RS
4. PA

Anthropometry

Height (cm) :-

Weight (kg) :- BMI =

Waist circumference (cm):- Hip circumference(cm):-

Waist hip ratio:

Investigations:

1.Fasting blood sugar:

2.Post prandial blood sugar:

3.HbA1C:

X

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Masterchart For GROUP B								0 Weeks			6 weeks		12 weeks			
Sr. No.	Reg. No.	Age	Sex	DM since	Height	Weight	BMI	FBS	PPS	Hb1	FBS	PPS	FBS	PPS	Hb1	V
1	103140003	56	M	2	1.73	67	22.39	190	282	9	114	148	108	140	6.8	
2	1704140016	58	M	2	1.69	70	24.51	146	289	9.1	107	170	100	170	6	
3	107140001	48	F	1	1.69	72	25.21	144	298	9.9	100	148	90	135	6.7	
4	207140046	42	F	1	1.69	59	20.66	176	267	9.4	98	150	90	150	6.8	
5	107140020	72	M	4	1.5	70	31.11	186	246	8.9	108	173	100	170	6	
6	208140010	60	M	3	1.67	60	21.51	178	234	9	109	164	100	160	6.8	
7	909140008	45	F	1	1.78	70	22.09	178	240	8.9	102	140	90	143	6.1	
8	109140023	55	M	2	1.56	60	24.65	164	246	8.4	108	172	94	164	6.2	
9	109140052	55	M	2	1.72	60	20.28	174	234	8.8	98	156	98	148	6.5	
10	112140032	73	M	4	1.67	60	21.51	184	256	9	98	156	98	147	6.3	
11	112140029	74	M	4	1.55	60	24.97	178	272	9	112	144	100	140	6	
12	302140035	76	M	5	1.55	60	24.97	170	312	9.3	112	140	100	140	6.5	
13	202140009	72	M	4	1.56	72	29.59	178	252	9.3	88	178	88	170	6.9	
14	304140017	75	M	4	1.67	60	21.51	208	248	9	118	146	118	150	6	
15	2804140046	54	M	3	1.78	56	17.67	165	318	9.7	92	143	92	143	6.9	
16	205140005	55	M	2	1.56	72	29.59	167	298	9	124	162	124	155	7	
17	205140052	44	F	1	1.75	70	22.86	156	312	8.4	108	154	108	154	6	
18	206140052	45	F	1	1.68	74	26.22	178	311	8.1	98	178	98	170	7.1	
19	407140002	54	M	2	1.8	78	24.07	140	272	8.7	102	134	102	134	6.5	
20	206140074	47	F	1	1.55	50	20.81	173	267	9	128	184	128	170	6.3	
21	707140062	56	M	2	1.49	78	35.13	168	256	9.7	110	154	110	154	6.2	
22	206140076	60	M	3	1.63	55	20.70	178	259	9.1	138	178	110	170	6.4	
23	610140033	64	M	4	1.56	72	29.59	184	345	8.7	110	148	110	148	6.4	
24	2008140002	74	F	1	1.75	70	22.86	210	312	9	132	168	132	165	7	
25	610140041	54	F	1	1.76	54	17.43	226	310	8.6	128	184	100	184	7	
26	210140015	58	M	3	1.6	68	26.56	140	264	8.8	110	189	110	170	6.7	
27	212140009	48	F	3	1.7	60	20.76	168	248	9.2	98	134	98	134	6	
28	302140006	52	M	3	1.72	58	19.61	186	254	9	104	167	104	160	7	
29	1711140020	48	F	1	1.65	68	24.98	210	308	9.4	130	178	110	178	6	

30	1003140004	54	M	3	1.5	56	24.89	167	312	9	84	167	84	167	6.4	
31	305140013	64	F	1	1.51	68	29.82	168	298	9.1	120	134	120	134	7.2	
32	306140047	68	F	1	1.8	64	19.75	158	278	9.2	114	146	114	140	6	
33	307140008	65	F	1	1.5	56	24.89	164	284	8.8	120	148	120	144	5.3	
34	308140001	62	F	1	1.57	68	27.59	163	278	8.4	104	156	104	150	7	
35	309140010	65	F	1	1.52	52	22.51	168	268	8.9	108	168	108	155	6.8	

MASTERCHART OF GROUP A (M+G)								BASELINE			6 WEEKS		12 WEEK			
Sr. No.	Reg No.	Age	Sex	DM since	Height	Weight	BMI	FBS	PPS	Hb1	FBS	PPS	FBS	PPS	Hb1	Wei
1	311140041	58	M	3	1.62	70	26.67	213	312	9.4	124	183	111	143	6.8	
2	404140020	67	M	4	1.56	78	32.05	170	289	8.6	107	176	107	176	6	
3	406140009	74	M	4	1.56	60	24.65	184	254	9.8	112	148	112	148	6.7	
4	407140046	72	M	4	1.51	55	24.12	172	363	9.4	118	156	98	156	6.8	
5	408140059	56	M	3	1.53	51	21.79	164	246	8.9	108	173	108	173	6	
6	409140021	59	M	3	1.47	60	27.77	178	234	9	109	178	109	164	6.8	
7	409140019	54	M	2	1.61	78	30.09	204	298	8.7	102	187	102	140	6.1	
8	1109140010	46	F	2	1.45	78	37.10	158	246	8.4	118	172	108	172	6.2	
9	304140018	74	M	4	1.67	53	19.00	174	244	8.8	124	156	98	156	6.5	
10	505140001	61	M	3	1.56	62	25.48	184	256	9.6	98	156	98	156	6.3	
11	1905140016	45	F	1	1.55	62	25.81	169	272	8	118	144	112	144	6	
12	906140038	55	M	3	1.6	47	18.36	228	312	9.3	112	197	112	140	6.5	
13	508140005	78	M	4	1.62	50	19.05	178	252	9.3	132	178	88	178	6.9	
14	508140008	62	M	3	1.63	70	26.35	164	248	9	118	167	118	146	6	
15	508140007	64	M	3	1.82	74	22.34	228	318	8.7	92	143	92	143	6.9	
16	508140018	45	F	1	1.45	78	37.10	256	340	8	138	162	124	162	6.9	
17	1011140038	61	M	3	1.65	70	25.71	148	243	8.4	108	154	108	154	6	
18	1511140036	46	F	1	1.59	70	27.69	132	254	8.1	100	188	98	178	7.1	
19	511140001	58	M	3	1.47	60	27.77	140	273	8	102	187	102	134	6.5	
20	1207140001	46	F	2	1.57	56	22.72	173	280	9.9	128	184	128	184	6.3	
21	605140003	54	M	2	1.53	51	21.79	168	264	9.7	110	168	110	154	6.2	
22	603150003	48	F	2	1.55	62	25.81	178	256	9.1	144	189	138	178	6.4	
23	2502150049	58	M	3	1.62	70	26.67	254	343	8.7	110	186	110	148	6.4	
24	801150002	65	F	1	1.7	57	19.72	184	216	8.8	136	164	132	168	7	
25	101150001	76	M	4	1.67	53	19.00	174	310	8.6	128	184	128	184	7	
26	201150020	55	F	1	1.65	60	22.04	140	278	8.8	104	204	110	189	6.7	
27	202150002	48	F	2	1.61	70	27.01	168	267	8.9	118	134	98	134	6	
28	203150006	44	F	1	1.63	70	26.35	178	284	9.8	112	150	104	167	7	

29	1603150004	45	F	1	1.57	64	25.96	210	311	9.4	144	198	130	178	6	
30	2802150002	52	F	2	1.6	76	29.69	246	343	9	84	167	84	167	6.4	
31	301150035	56	F	1	1.62	60	22.86	143	273	8.4	118	140	120	134	7.2	
32	403150007	58	F	1	1.8	61	18.83	140	188	8.2	118	146	114	146	6	
33	502150001	60	F	1	1.7	70	24.22	144	180	8.1	134	148	120	148	5.3	
34	603150004	64	F	1	1.8	61	18.83	156	190	7.9	108	156	104	156	7	
35	603150043	78	F	1	1.63	62	23.34	167	243	7.4	110	168	108	168	6.8	

Masterchart For GROUP B								0 Weeks			6 weeks		12 weeks			
Sr. No.	Reg. No.	Age	Sex	DM since	Height	Weight	BMI	FBS	PPS	Hb1	FBS	PPS	FBS	PPS	Hb1	V
1	103140003	56	M	2	1.73	67	22.39	190	282	9	114	148	108	140	6.8	
2	1704140016	58	M	2	1.69	70	24.51	146	289	9.1	107	170	100	170	6	
3	107140001	48	F	1	1.69	72	25.21	144	298	9.9	100	148	90	135	6.7	
4	207140046	42	F	1	1.69	59	20.66	176	267	9.4	98	150	90	150	6.8	
5	107140020	72	M	4	1.5	70	31.11	186	246	8.9	108	173	100	170	6	
6	208140010	60	M	3	1.67	60	21.51	178	234	9	109	164	100	160	6.8	
7	909140008	45	F	1	1.78	70	22.09	178	240	8.9	102	140	90	143	6.1	
8	109140023	55	M	2	1.56	60	24.65	164	246	8.4	108	172	94	164	6.2	
9	109140052	55	M	2	1.72	60	20.28	174	234	8.8	98	156	98	148	6.5	
10	112140032	73	M	4	1.67	60	21.51	184	256	9	98	156	98	147	6.3	
11	112140029	74	M	4	1.55	60	24.97	178	272	9	112	144	100	140	6	
12	302140035	76	M	5	1.55	60	24.97	170	312	9.3	112	140	100	140	6.5	
13	202140009	72	M	4	1.56	72	29.59	178	252	9.3	88	178	88	170	6.9	
14	304140017	75	M	4	1.67	60	21.51	208	248	9	118	146	118	150	6	
15	2804140046	54	M	3	1.78	56	17.67	165	318	9.7	92	143	92	143	6.9	
16	205140005	55	M	2	1.56	72	29.59	167	298	9	124	162	124	155	7	
17	205140052	44	F	1	1.75	70	22.86	156	312	8.4	108	154	108	154	6	
18	206140052	45	F	1	1.68	74	26.22	178	311	8.1	98	178	98	170	7.1	
19	407140002	54	M	2	1.8	78	24.07	140	272	8.7	102	134	102	134	6.5	
20	206140074	47	F	1	1.55	50	20.81	173	267	9	128	184	128	170	6.3	
21	707140062	56	M	2	1.49	78	35.13	168	256	9.7	110	154	110	154	6.2	
22	206140076	60	M	3	1.63	55	20.70	178	259	9.1	138	178	110	170	6.4	
23	610140033	64	M	4	1.56	72	29.59	184	345	8.7	110	148	110	148	6.4	
24	2008140002	74	F	1	1.75	70	22.86	210	312	9	132	168	132	165	7	
25	610140041	54	F	1	1.76	54	17.43	226	310	8.6	128	184	100	184	7	
26	210140015	58	M	3	1.6	68	26.56	140	264	8.8	110	189	110	170	6.7	
27	212140009	48	F	3	1.7	60	20.76	168	248	9.2	98	134	98	134	6	
28	302140006	52	M	3	1.72	58	19.61	186	254	9	104	167	104	160	7	
29	1711140020	48	F	1	1.65	68	24.98	210	308	9.4	130	178	110	178	6	

30	1003140004	54	M	3	1.5	56	24.89	167	312	9	84	167	84	167	6.4	
31	305140013	64	F	1	1.51	68	29.82	168	298	9.1	120	134	120	134	7.2	
32	306140047	68	F	1	1.8	64	19.75	158	278	9.2	114	146	114	140	6	
33	307140008	65	F	1	1.5	56	24.89	164	284	8.8	120	148	120	144	5.3	
34	308140001	62	F	1	1.57	68	27.59	163	278	8.4	104	156	104	150	7	
35	309140010	65	F	1	1.52	52	22.51	168	268	8.9	108	168	108	155	6.8	